Active Metal Template Synthesis of Rotaxanes, Catenanes and Knots

Paul R. McGonigal

Degree of Doctor of Philosophy

School of Chemistry
University of Edinburgh

August 2010

Dedicated to my Family

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Abstract

The use of a chemical template to control the spatial arrangement of reactants revolutionized the synthesis of mechanically interlocked molecules.[1] The recently developed 'active metal template' strategy,[2] in which transition metal ions act as both the template to guide interlocking and as the catalyst for the covalent bond forming reaction that captures the interlocked structure, has several advantages in comparison with traditional 'passive template' approaches.

In contrast with passive template approaches the active template strategy is more efficient, completing the assembly of the interlocked structure in one step instead of two and in some cases requiring only a substoichiometric amount of metal template. In addition, fewer permanent recognition sites are required and in certain cases the active template reaction can shed light on mechanistic details of related metal-catalyzed processes and act as a conduit for reaction discovery.

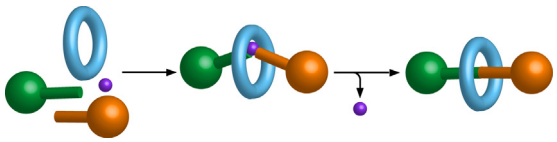

Figure 1. Schematic representation of the active metal template synthesis of [2]rotaxanes.

This Thesis will discuss the expansion of this new methodology in two main directions: firstly, exploration of new active metal template reactions, specifically the application of a novel Ni catalyzed sp^3–sp^3 C–C bond forming reaction,[3] and secondly, the application of previously developed active template reactions to the synthesis of agrochemical-based [2]rotaxanes and other architectures, macrobicyclic [3]rotaxanes,[4] [2]catenanes[5] and a trefoil knot.

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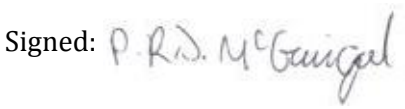
4. Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315–320.
5. Goldup, S. M.; Leigh, D. A.; Long, T.; McGonigal, P. R.; Symes M. D.; Wu, J. *J. Am. Chem. Soc.*, **2009**, *131*, 15924–15929.

Declaration

The scientific work described in this Thesis was carried out in the School of Chemistry at the University of Edinburgh between September 2007 and July 2010. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification at this or any other University or institute of learning.

Signed: 

Date: 24th November 2010

Lectures and Meetings Attended and Presentations Given

1. Organic Research Seminars, School of Chemistry, University of Edinburgh, UK, 2007-2010.

Oral Presentations

a) *Rotaxanes with biologically active motifs*, November 2007.

b) *Extension of the active template methodology*, March 2009.

2. School of Chemistry Visiting Speaker Colloquia, School of Chemistry, University of Edinburgh, UK, 2007-2010.

3. RSC Perkin Division 35th Scottish Regional Meeting, University of Glasgow, UK, December 2007.

4. Avance/Topspin Training Course, Bruker Biospin Ltd., Coventry, UK, February 2008.

5. Chemical Sciences Scotland Future Forum, Scottish Enterprise Forth Valley, Laurel House, Stirling, UK, September 2008.

6. Reinhoudt Group Work Week Symposium, School of Chemistry, University of Edinburgh, UK, November 2008.

Poster presentation: *Extension of the active template methodology to the synthesis of novel architectures.*

7. RSC Perkin Division 36th Scottish Regional Meeting, University of Aberdeen, UK, December 2008.

Poster presentation: *Extension of the active template methodology to the synthesis of novel architectures.*

7. School of Chemistry, Organic Section Firbush Symposium, Firbush Point Centre, University of Edinburgh, UK, April 2009.

Poster presentation: *Doubly threaded [3]rotaxanes from a single active template binding site.*

8. 42nd IUPAC Meeting 2009, SECC, Glasgow, UK, August 2009.
Poster presentation: *Doubly threaded [3]rotaxanes from a single active template binding site.*

9. RSC Perkin Division 37th Scottish Regional Meeting, University of Strathclyde, UK, December 2008.
Poster presentation: *Active Metal Template Synthesis of Interlocked Architectures.*

10. School of Chemistry, Organic Section Firbush Symposium, Firbush Point Centre, University of Edinburgh, UK, April 2010.
Oral presentation: *Active metal template synthesis of rotaxanes, catenanes and knots.*

11. 5th International Symposium on Macrocyclic & Supramolecular Chemistry, Nara Prefecture, Japan, June 2010.
Poster presentation: *Active Metal Template Synthesis of Interlocked Architectures.*
Wiley Poster Prize – 1st place.

12. 12th Belgian Organic Synthesis Symposium, Namur, Belgium, July 2010.

Acknowledgements

The first thanks must go to the commander-in-chief of the Archibald Scott Couper lab, Prof. David Leigh, for allowing me the privilege of working in such a fantastic environment over the past few years and providing all the resources I ever needed and a constant supply of charismatic co-workers. Perhaps most importantly, he introduced me to a fascinating area of chemistry and gave me freedom and independence to explore it. Special thanks also go to Dr. Steve Goldup for providing me with inspiration and invaluable guidance, for teaching me, and for keeping Britpop high on the Leigh group play list. I would also like to thank all of the other talented scientists I have been lucky enough to work closely with and without whom this Thesis would not exist; specific contributions are highlighted at the start of each chapter.

My period in the Leigh group has been a time of learning and hard work but also of great enjoyment, for that I would like to thank all the people that have kept me entertained over the years. Anthony "Fingers of Fury" Fernandes and Dominik for many Saturday afternoons spent playing guitar together and the other members of the Leigh Group band 'The Overdrivers'; our magnetic front man Edzard, Anne-Celine, Spud, Adam and the two Steves on skins. Our first gig together in KB house and the conception of our Rolling Stones medley are particularly special memories. I also have fond memories of the ChemSoc football league, thanks to my team mates during our championship winning season as Victorious Secret; Edzard, Max, Alex, TurboAd, David S, Steve and Mike. Also our rivals River Hotplate, the members of our sister team the Leigh Group Galaxy and team mates from Bayern Bru during the subsequent hard-fought seasons as runners up. Thanks to the many regular participants of 'Tuesday football' at Meadowbank who helped me to miraculously assemble 14 players each week and for tolerating my erratic form.

I would also like to thank my fellow 'NMR chimps'; Mark for teaching me to the art of spectrometer maintenance, Max for sharing the burden, and the new generation, Adam and Bartek for relieving me of my duty. On the many occasions that our collective knowledge was insufficient we were extremely fortunate to be able to turn to the heroic talents of Juraj Bella.

I would also like to thank all the other past Leigh group members; Bryan, Vicki “Big Ron” Ronaldson, James C, Pepe, Satoshi, Nick, Kevin, Aurélien, Romen, Barry-san, Roy, Christiane, Paul L, Tao, Costanza, Ai-Lan, Diego, Euan, Anne-Marie, Smilja, Chin-Fa, Monica, Luciana, Nathalie, James B, Hei Man, Francesca, Takeshi, Luca, Teresa and others I have surely forgotten as well as those that are still here and have put up with me during ‘the Thesis months’; Bea, Armando “Il Pagliaccio” Carlone, Kathleen, Phill, Jon, Victor, Maria, Marcus, Francesco, Dave H, Ara, Ula, Patrick, Daniel, Chris, Jhenyi, Marius, Max and Adam. Louise and Stewart have provided first class technical support over the years, thanks to them and all the support staff in the Joseph Black Building.

Thanks to Jagger & Richards, Lennon & McCartney, Weller, Ashcroft, Casblancas, Turner, the Gallaghers, the Followills, Bowie, Meighan & Pizzorno, White, Townsend & Daltrey, Gervais, Merchant & Pilkington and the other inhabitants of my iPod that have provided the backdrop to many long hours spent standing at fumehood 12 and to the Deuchars in KB house for easing the pain of many long columns and the ringing in my ears after Marius’ drum and bass Fridays.

An honourable mention must go to Sandy McLeman, my simply excellent high school chemistry teacher that instilled a passion for chemistry in me. Also to high school and university friends that have kept me sane along the way; Martin, Spud, Chris, Togher, Kev, Dave and Mark “Greggs Bag” McConnell.

I owe a lot to my parents, Ruth and Stephen for their unwavering support throughout my entire education. Then there’s Adam, Emma, Kenny, Martine and my Grandparents who have helped me whenever I’ve needed it and the latest additions, Mairi and Anna. This Thesis is for you guys.

Finally and most importantly, I would like to thank Mary for teaching me to (almost) speak Italian, the simple pleasure of homemade bruschetta and lasagne, for persuading me to spend time away from the lab when I needed it and for her continued love and support.

Abbreviations

Ac	Acetyl
AI	Active ingredient
AMT	Active metal template
APCI	Atmospheric pressure chemical ionisation
Boc	*tert*-Butyloxycarbonyl
b.p.	Boiling point
br	Broad
Bu	Butyl
calcd.	Calculated
cat.	Catalytic amount
CD	Cyclodextrin
cod	Cyclooctadiene
CPK	Corey–Pauling–Koltun space filling model
CuAAC	Cu^{I}-catalyzed 1,3-cycloaddition of terminal alkynes with azides
Cy	Cyclohexyl
d	Doublet
2,4-D	2,4-Dichlorophenoxyacetic acid
dec.	Decomposes
DB-[24-C-8]	Dibenzo-24-crown-8
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dpp	2,9-Diphenyl-1,10-phenanthroline
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

EDTA	Ethylenediaminetetraacetic acid
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FAB	Fast atom bombardment
GCMS	Gas chromatography-mass spectrometry
HOBt	1-Hydroxybenzotriazole
HR	High resolution
IPA	Isopropyl alcohol
LiHMDS	Lithium bis(trimethylsilyl)amide
LR	Low resolution
m	Multiplet
Me	Methyl
MIM	Mechanically interlocked molecule
M.p	Melting point
MS	Mass spectrometry
NBS	N-bromosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
3-NOBA	3-Nitrobenzyl alcohol
P	Partition coefficient (octanol/water)
PEPPSI	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Petrol	Petroleum ether boiling in the range 40-60 °C
Ph	Phenyl
Pr	Propyl
p-Tol	p-Tolyl (4-$CH_3C_6H_4$-)
pybox	Pyridine-2,6-bisoxazoline
q	Quartet
quant.	Quantitative

quint.	Quintet
RCM	Ring closing olefin metathesis
rt	Room temperature
s	Singlet
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
terpy	2,2':6',2"-Terpyridine
Tf	Trifluoromethanesulfonyl (Triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THIOG	Thioglycerol
TLC	Thin-layer chromatography
Ts	*para*-Toluenesulfonyl (Tosyl)
UV	Ultraviolet

Note: conventional abbreviations for units, physical quantities and stereochemical terms are not included here.

General Comments on Experimental Data

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Dry CH_2Cl_2, THF, $CHCl_3$, acetonitrile and DMF were obtained by passing the solvent through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Flash column chromatography was carried out using Kiesegel C60 (Fisher) as the stationary phase, preparative TLC was carried out using precoated silica gel plates (2000 microns thick, Silica gel GF, Uniplate, Germany) or precoated neutral alumina plates (0.25 mm thick, 60F254, Merck, Germany). Analytical TLC was performed on precoated silica gel plates (0.25 mm thick, 60F254, Merck, Germany) and observed under UV light. Preparative size exclusion chromatography was carried out using Bio-Rad S-X1 beads (40–80 μm bead size, 600–14,000 MW exclusion range) swollen in CH_2Cl_2. Preparative HPLC was performed on a Gilson Inc., USA instrument with a reversed-phase column (Ascentis® C18, 250 x 21.2 mm, 5 μm particle size, 15 mL/min flow rate). Microwave reactions were performed using a CEM Microwave Technology (Buckingham, UK) Discover apparatus, in Open Vessel mode and under one atmosphere of nitrogen. All ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 or AV 500 (cryoprobe) instruments, at a constant temperature of 300 K. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz). All ^{13}C NMR experiments were proton decoupled. Assignment of the ^{1}H NMR signals was accomplished by two-dimensional NMR spectroscopy (COSY, TOCSY, NOESY, HSQC, HMBC). All melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. LRESI-MS was performed with a Micromass Platform II mass spectrometer, controlled using Masslynx v2.3 software or on an Agilent Technologies 1200 LC system with 6130 single quadrupole MS detector (APCI or ESI source). HR-MS data was obtained from the EPSRC National Mass Spectrometry Service Centre (Swansea, U.K.) and the services at The University of Edinburgh.

Thesis Layout

Chapter 1 provides an introduction to mechanically interlocked molecules, their conception, initial synthetic efforts and the variety of modern day template approaches by which they can be accessed. In the interests of brevity and relevance to this Thesis only metal template methods are discussed in detail, other template approaches are addressed more briefly in an effort to provide some wider context to subsequent discussions without offering superfluous detail. Chapters 2, 3 and 4 are each presented in the form of articles which have recently been published in peer-reviewed journals. No attempts have been made to rewrite this work out of context, however minor aesthetic alterations have been made in the interest of consistency throughout the Thesis. The corresponding original papers are reproduced in their original format in the Appendix. Chapter 5 discusses the ongoing investigation of active template synthesis of a trefoil knot. Finally, Chapter 6 describes work carried out in collaboration with *Syngenta* towards the design, synthesis and assessment of agrochemical-based rotaxanes.

CHAPT. 1 | TEMPLATE STRATEGIES FOR THE SYNTHESIS OF INTERLOCKED MOLECULES

Synopsis

This introductory Chapter focuses first of all on the concept of mechanically interlocked molecules (MIMs), molecular knots and the associated nomenclature employed throughout this Thesis to describe various different structures. This is followed by discourse on the early examples of synthetic MIMs assembled using statistical threading and covalent directed syntheses. Modern template strategies are then discussed starting with a brief introduction to chemical templates and some general principles behind their use. Different template interactions are then addressed individually. However, in the interests of brevity and relevance to this Thesis, only metal template methods are discussed in detail, other template approaches are addressed more briefly in an effort to provide some wider context to subsequent discussions without offering superfluous detail. The 'active' metal template (AMT) approach is considered in the greatest detail owing to its obvious importance to the Chapters that follow.

1.1 Mechanically Interlocked Molecules and Molecular Knots

Mechanically interlocked molecules (MIMs) are a class of molecules consisting of components which are held together not by covalent bonds or supramolecular interactions, but rather by 'mechanical bonds'. The nature of this mechanical bond is such that these components cannot be separated from one another without the cleavage of at least one covalent bond, consequently MIMs are categorized as true molecules rather than supramolecular species.[1] To describe the mechanical bond it is perhaps easiest to consider the simple analogy of the two interlocked links of a chain – there is no 'physical' connection between the two links but they are locked together, to separate them from one another one of the rings must be broken. This 'invisible bond' between two links of a chain could be said to be a result of their relative arrangement in space and the structural integrity of the links themselves. In a similar manner a mechanical bond is the result of the relative spatial arrangement of the components of a MIM and the inability of covalent bonds to pass through one another, locking the components together as in the chain. The possibility of the existence of MIMs was first put forward in the early 20th century; according to Vladimir Prelog, Richard Willstätter first discussed the idea of interlocked macrocyclic rings during a seminar in Zurich sometime between 1900 and 1912.[2] It wasn't until after the first synthesis of a catenane[3] by Wasserman in 1960 that the first theoretical written discussion on "Chemical Topology" was published.[2a] This seminal article by Frisch and Wasserman proposed that structures such as catenanes, rotaxanes, Möbius strips and molecular trefoil knots could be kinetically stable and synthetically accessible.

Cartoon representations of two of the most widely studied classes of MIMs are shown in Figure 1.1 (a and b). A catenane (from the Latin *catena* meaning chain) consists of two or more interlocked rings whereas a rotaxane (from the Latin *rota* meaning wheel and *axis* meaning axle) consists of a ring held on a linear unit (also known as a thread, axle or dumbbell) by two bulky stoppering groups.

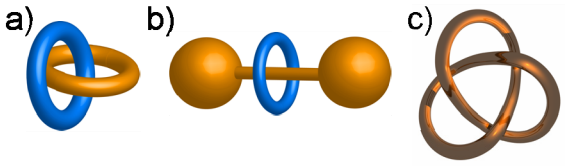


Figure 1.1. Schematic representations of a) a catenane, b) a rotaxane and c) a trefoil knot.

Catenanes display non-trivial topology; in mathematical terms the molecular graph of a catenane is non-planar. More simply put these structures cannot be drawn on a sheet of paper without crossing points.[4] Molecular knots constitute another class of molecules which can be described as topologically non-trivial.[5] A molecular knot is a kinetically stable entanglement constructed from a single closed curve. The simplest example of a non-trivial knot[6] contains three crossing points and is known as a trefoil knot (Figure 1.1c). Due to the similarity between MIMs and molecular knots in terms of the means by which they are synthesized, these two classes of structures are often considered together and will be discussed concurrently throughout the rest of this Chapter.

1.2 Nomenclature

By convention, the nomenclature for the naming of MIMs is largely determined by the topology of the species and the number of mechanically bound components. In the case of rotaxanes and catenanes a prefix is attached in square brackets indicating the number of components, regardless of their connectivity.[2b] For example, a [6]catenane would be a system of 6 rings held together by mechanical bonds, however these could be linked in a variety of ways giving rise to topological isomerism (Figure 1.2).

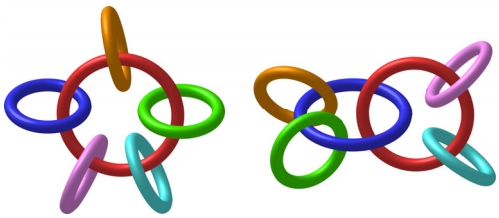


Figure 1.2. Topological isomerism – two of the many possible arrangements of rings that could be termed a [6]catenane.

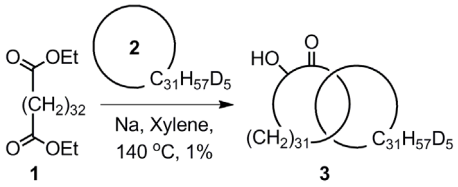
Naming of [*n*]rotaxanes is even more ambiguous with the additional variable that the components may be either an axle or ring; for example the term [3]rotaxane could be applied to both a species with two rings trapped around a single thread or with one ring trapped around two threads. This nomenclature is employed throughout this Thesis and wherever there is the possibility of ambiguity between topologies it is hoped that the associated Schemes and Figures will clarify the intended meaning.

1.3 Early Synthetic Methods

1.3.1 Approaches Involving Randomness

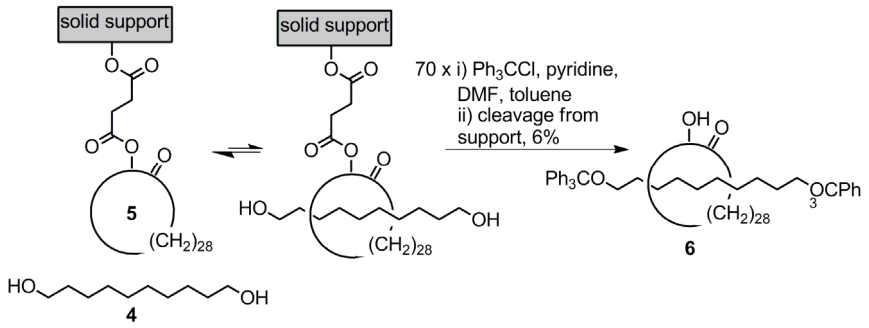
The genesis of MIMs as a synthetic area came in 1960 when Wasserman published the first synthesis of a [2]catenane. Wasserman relied on the random threading of a macrocycle precursor, diethyl tetratriacontanedioate **1**, through macrocyclic hydrocarbon **2** prior to cyclization to create the interlocked rings (Scheme 1.1). Despite using the macrocyclic hydrocarbon **2** in huge excess (as 50% of the solvent mixture), the target catenane **3** was isolated in less than 1% yield.[7] However, even with the low yield this was a massive achievement not least because of the difficulty of characterizing the isolated catenane.[8]

Scheme 1.1. Wasserman's synthesis of a catenane via statistical threading.



Subsequently, Wolovsky and Wasserman undertook an alternative statistical strategy for the construction of two interlocked rings; they postulated that the random formation of a Möbius strip-type intermediate by twisting of cyclododecene prior to olefin metathesis reaction would lead to the formation of a [2]catenane. Both Wolovsky and Wasserman simultaneously reported mass spectroscopy evidence in support of the formation of their target structure. However, neither reported yields as the amount of [2]catenane in the crude reaction mixture was, presumably, immeasurably small and therefore unisolable.[9] It was another seven years before the next milestone was reached, synthesis of the first rotaxane.[10] Harrison and Harrison applied a statistical threading approach as Wasserman had done before, relying solely on random, unlikely threading events of a linear diol **4** when washed down a column of a resin-bound macrocycle **5**. Capping of the thread was achieved via a nucleophilic substitution reaction with bulky trityl chloride and the free rotaxane **6** was liberated by cleavage from the solid support. Once again, a meager amount of interlocked product was isolated, just 6% after 70 iterations, demonstrating the poor efficiency of a probability-based strategy for the synthesis of MIMs. Although improvements in the statistical threading approach by Zilkha led to yields of up to 15%,[11] clearly, if the properties of interlocked systems were to be fully explored more efficient methods by which to synthesize MIMs would be required.

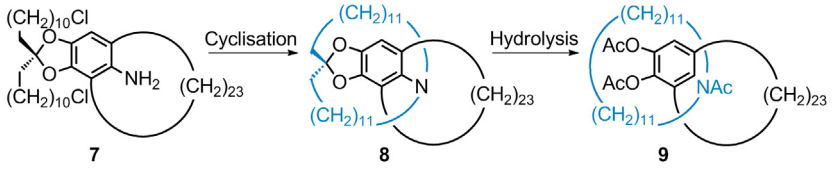
Scheme 1.2. Synthesis of the first rotaxane relying on statistical threading.



1.3.2 Covalent Template Directed Synthesis

The major drawback of earlier synthetic approaches involving randomness was the lack of a directing force towards the formation of an interlocked species. In 1964 Schill was the first to attempt to make use of a template with a view to increasing the efficiency of catenane synthesis.[12] In the words of Daryl Busch, chemical templates '*organize an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms.*'[13] The key feature of Schill's 'covalent template' method was the use of a carefully constructed covalent scaffold such as **7** which, due to the restriction of bond angles and chain lengths, was predisposed to form an interlocked structure upon cyclization, avoiding extra-annular ring closures (Scheme 1.3).[14]

Scheme 1.3. Schill's covalent directed synthesis of a [2]catenane.



In spite of the elegant designs employed, the covalent directed approach towards the synthesis of MIMs suffered from low overall yields of typically less than 1% as a lengthy synthesis was required in order to access the key cyclization precursor. The use of a rigid covalent skeleton to facilitate interlocking was evidently problematic. However, the concept of profiting from a chemical template has ultimately proven to be advantageous.

1.4 Supramolecular Template Directed Synthesis

Ideally, to achieve high yields of the desired MIMs, there should be some kind of driving force towards interlocking.[1b] A mutually attractive interaction between the components of a potentially interlocked structure could, if sufficiently strong and appropriately orientated, act as this guiding force. Non-covalent interactions could take the role of the attractive force, allowing construction of the interlocked structure around a central site—as in the covalent directed synthesis—but with all the added benefits of molecular self-assembly. In short, the use of a supramolecular chemical template can afford highly efficient access to MIMs.

The first landmark achievement in this arena came from Jean-Pierre Sauvage in 1983. Taking advantage of the coordination geometry of a metal ion to template catenane formation,[15] this advance allowed ready access to MIMs in high yields with relatively little synthetic effort and is undoubtedly responsible for turning the field of MIMs from an academic curiosity into the vast area of research it is today. Efficient access to MIMs using supramolecular chemical templates opened up these intriguing structures to investigation as novel materials,[16] components in molecular devices,[17] drug delivery systems[18] and molecular electronics.[19] In addition to metal ion coordination (Section 1.4.2) other non-covalent interactions such as hydrogen bonding (Section 1.4.1.1), hydrophobic effects (Section 1.4.1.2) and donor–acceptor aromatic interactions (Section 1.4.1.3) may also be used as the molecular 'glue' to hold different covalently bound components in a given orientation. More recently the active metal template method (AMT, Section 1.4.3) has been pioneered; uniquely in this strategy the template plays a role in the covalent capture of the MIM on top of acting as the guiding force.

Strategically, there are two classical ways by which to build a MIM around a central template – either via a 'clipping' strategy or via a threaded pseudorotaxane intermediate (Figure 1.3). Construction of a [2]catenane in the clipping strategy

(Figure 1.3a, i) necessitates the association of two linear macrocyclic precursors prior to a double cyclization.[20] The corresponding clipping synthesis of a [2]rotaxane (Figure 1.3b, i) requires a template interaction between a dumbbell and a macrocyclic precursor followed by cyclization around the thread.[21] Alternatively, a pseudorotaxane complex can be formed by means of non-covalent interactions between the endotopic binding site of a preformed macrocycle and a binding site on a linear thread, a catenane can then by generated by cyclization of the linear moiety ('threading-followed-by-clipping, Figure 1.3a, ii) whereas 'stoppering' the thread yields rotaxane ('threading-followed-by-stoppering, Figure 1.3b, ii).[22]

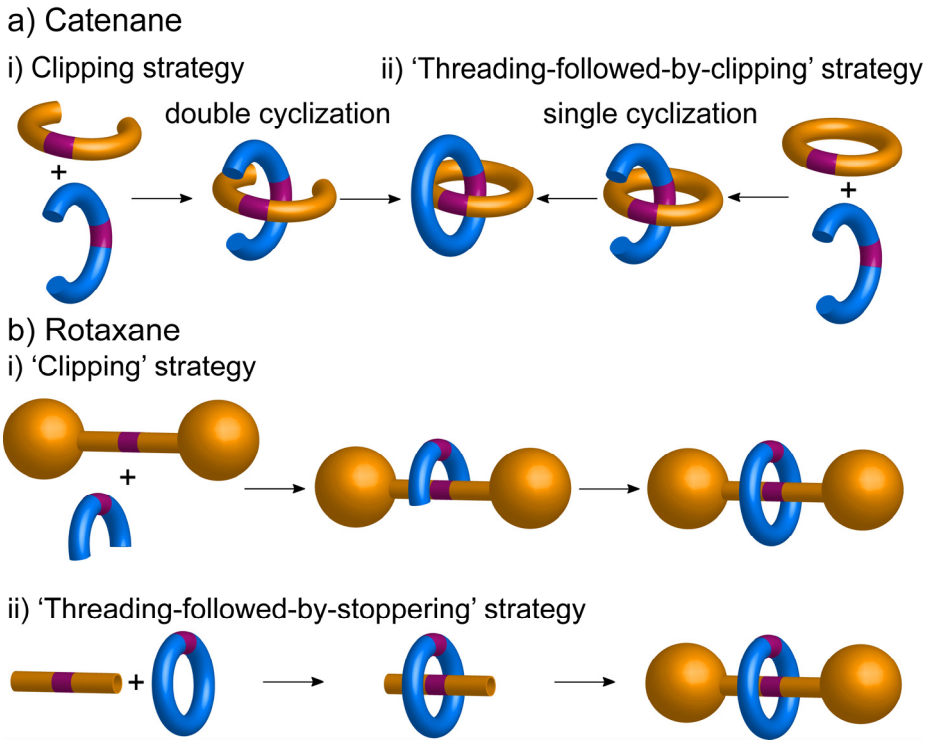


Figure 1.3. Strategies for the template assembly of MIMs – intercomponent non-covalent interactions depicted as complementary purple binding sites.

1.4.1 Non-Transition Metal Templates

1.4.1.1 Hydrogen Bonding Interactions

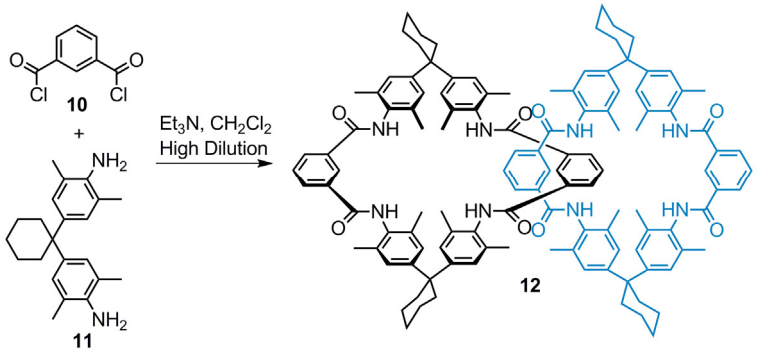
The reversible nature and directionality of hydrogen bonding are ideally suited for use as in chemical templates, although a single hydrogen bond is, generally speaking,

many times weaker than a covalent bond or metal–ligand bond and weaker than the average thermal energy available to break them. Consequently hydrogen bond templates typically utilize multipoint hydrogen bonding motifs with a high degree of preorganization.

A) AMIDE-BASED TEMPLATES

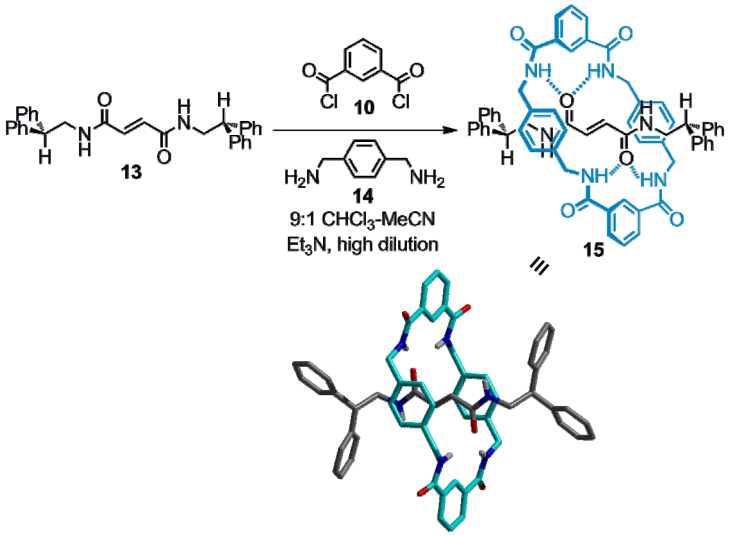
In 1992, Hunter serendipitously achieved the first hydrogen bond templated synthesis of an amide catenane while trying to improve the yield of a macrocycle forming reaction (Scheme 1.4).[23] The one-pot double macrocyclization process resulted in 34% of [2]catenane **12** due to a supramolecular self-assembly process – multipoint hydrogen bonding directed the formation of two interlocking rings.

Scheme 1.4. Hunter's synthesis of an amide catenane.



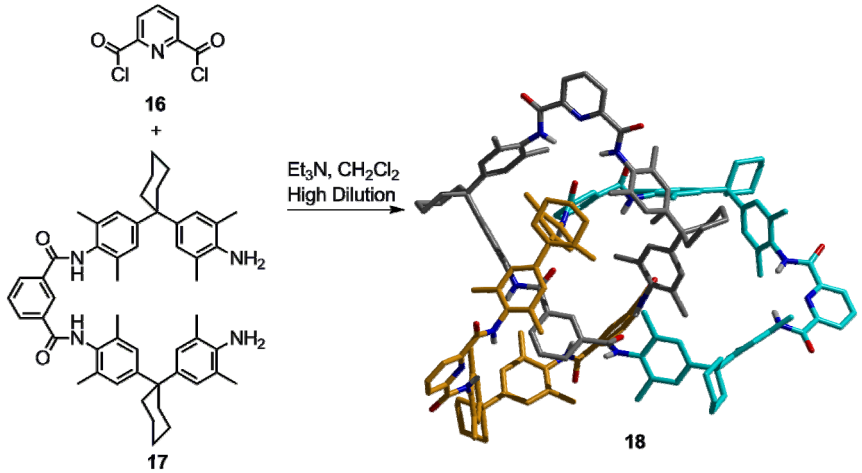
Since then, similar amide hydrogen bonding motifs have found widespread use. In 1995, Leigh and co-workers reported a protocol to synthesise a benzylic amide [2]catenane via reaction of isophthaloyl dichloride **10** and para-xylylenediamine **14**, also discovered by chance.[24] It was postulated that complementary hydrogen bonding between short oligomers in solution stabilize macrocycle and ultimately [2]catenane formation. Leigh later discovered that by inclusion of an amide-bearing dumbbell in the reaction mixture the amide rings could form around the thread to produce [2]rotaxane.[25] By improving the rigidity and preorganization of the template site on the dumbbell increased yields could be obtained.[26] When a fumaramide template site was used, the near perfect preorganization for the benzylic amide macrocycle led to an incredible 97% yield of rotaxane **15** (Scheme 1.5).[26b]

Scheme 1.5. Leigh's rigid fumaramide hydrogen bond template.



In addition to efficient, occasionally serendipitous, syntheses of MIMs, another chance discovery showed that molecular knots could also be constructed around the template affect of amide hydrogen bonding.[27] Vögtle, while attempting to assemble [n]catenanes from 2,6-pyridinedicarboxylic acid dichloride **16** and a diamine **17**, unexpectedly isolated molecular trefoil knot **18** in 20% (Scheme 1.6). This unusual outcome was confirmed by crystallographic analysis of the solid-state structure.

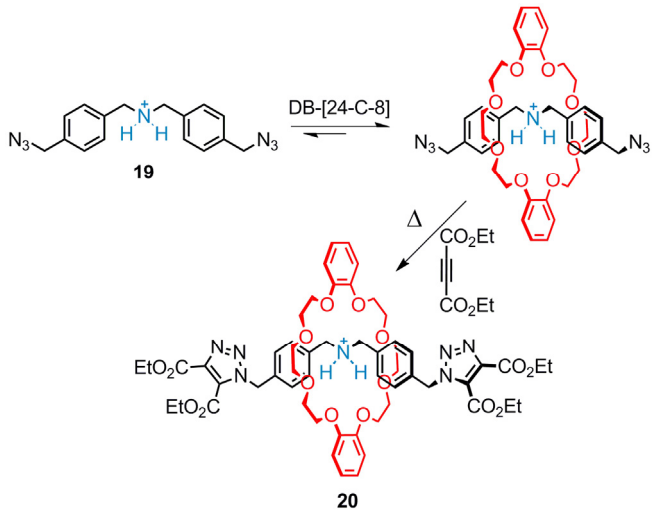
Scheme 1.6. Hydrogen bond directed synthesis of a trefoil knot.



B) AMMONIUM–CROWN ETHER TEMPLATES

Nobel laureate Charles Pederson was the first to discover that cyclic polyethers form stable inclusion complexes with metal salts and ammonium cations.[28] Subsequently crown ethers have been widely used as the macrocyclic component of rotaxanes due to their ability to form host–guest complexes with alkylammonium or pyridinium cations. The multiple acceptor atoms of the crown ethers readily form multipoint hydrogen bonds with an ammonium thread and stoppering of the inclusion complex covalently captures the MIM.[29,30] In 1995, Busch reported on pseudorotaxane formation at a solvent interface using such an ammonium–crown ether template, the cyclic polyether macrocycle threaded onto a 'bifunctional axle' which could be stoppered to capture the interlocked rotaxane structure. Soon afterwards Stoddart and co-workers made use of a similar secondary ammonium–crown ether template motif for the assembly of [2]– and [3]rotaxanes (Scheme 1.7).

Scheme 1.7. Stoddart's [2]Rotaxane synthesis with an ammonium–crown ether template.

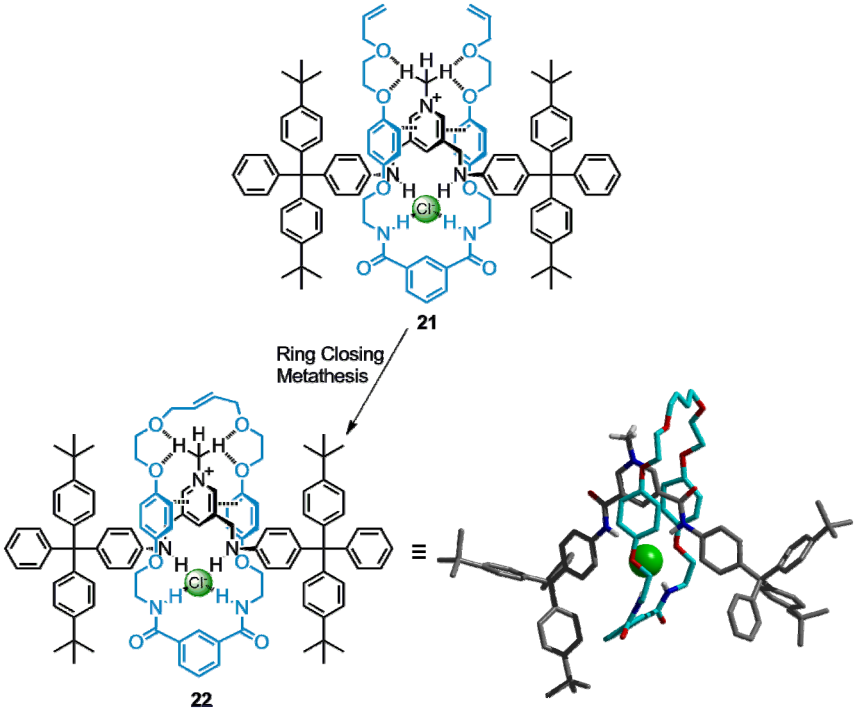


C) ANION-BASED TEMPLATES

A large variety of organic and inorganic structures have been assembled under the directing influence of anions. However, somewhat surprisingly, anion templates have only recently garnered significant interest in the synthesis of MIMs.[31] Vögtle reported the first instance of a [2]rotaxane assembled around an anionic phenolate template; an

amide macrocycle encapsulated a mono-stoppered phenolate thread which then participated in a S_N2 stoppering reaction to complete assembly of the MIM.[32] Beer and co-workers have studied construction of MIMs around chloride ions.[33] In one such example a clipping strategy using ring closing metathesis (RCM) mediated by Grubbs' catalyst afforded [2]rotaxane **22** in a 47% yield (Scheme 1.8).[33a]

Scheme 1.8. Beer's chloride ion directed assembly of a [2]rotaxane.



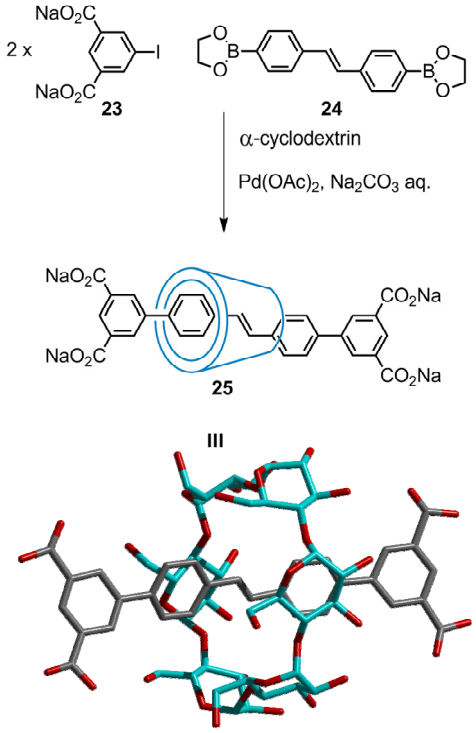
In addition to the hydrogen bonding interactions, the electrostatic interaction of the chloride–pyridinium close ion pair contributes substantially to the template effect. Beer applied a similar chloride–pyridinium motif in the synthesis of a catenane[33b] and in 2008 reported the sulfate anion templated clipping synthesis of a [2]catenane in a remarkable 80% yield.[34]

1.4.1.2 Hydrophobic Interactions

In aqueous media non-polar molecules tend to form aggregates driven by the entropic cost of cavity formation in the bulk solvent. Cyclodextrins (CDs)—cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucopyranose—are rigid, cone-shaped macrocycles with a hydrophobic cavity and a hydrophilic exterior so are

ideally suited to encapsulate non-polar guests. Stoppering at each end of linear, lipophilic guest molecules can capture a rotaxane architecture[35] – CD rotaxanes have been devised for a number of applications including protection or modification of dyes[36] and photochemically switchable molecular shuttles.[37] Anderson and co-workers reported the synthesis of highly fluorescent cyclodextrin–stilbene rotaxanes, stoppering of the stilbene thread was achieved via an aqueous Suzuki coupling (Scheme 1.9).[36a]

Scheme 1.9. Anderson's synthesis of a fluorescent-axle rotaxane.

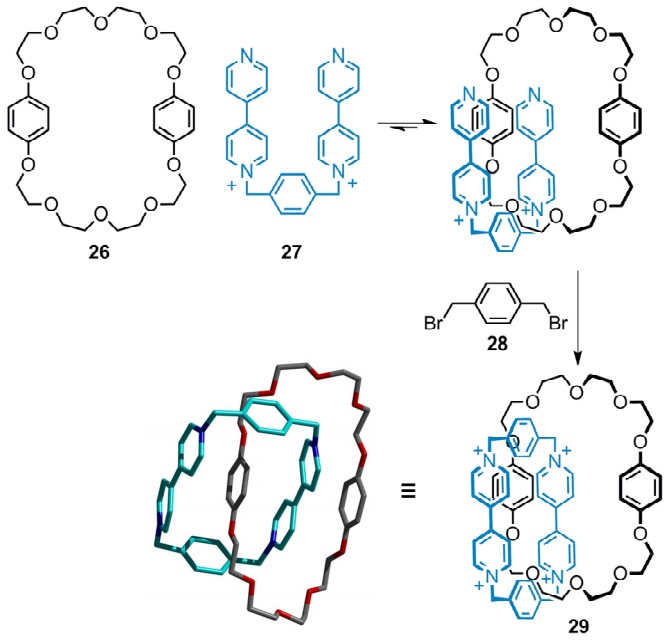


1.4.1.3 Donor–Acceptor Aromatic Interactions

Much of the seminal research in the area of MIMs assembled using aromatic interactions as the guiding template has been carried out by Stoddart and co-workers.[38] In the 1980s they reported the formation of an inclusion complex between paraquat, a π-electron deficient guest, and a π-electron rich cyclophane.[39] Recognising the potential of this interaction for application in the synthesis of MIMs, Stoddart went on to apply this template to the synthesis of a [2]catenane (Scheme 1.10).[40] Subsequently, similar donor–acceptor templates have been used in the

construction of other architectures including a molecular trefoil knot,[41] [n]catenanes,[42] and the first stimuli responsive molecular shuttle.[43]

Scheme 1.10. Donor–acceptor template synthesis of a catenane.



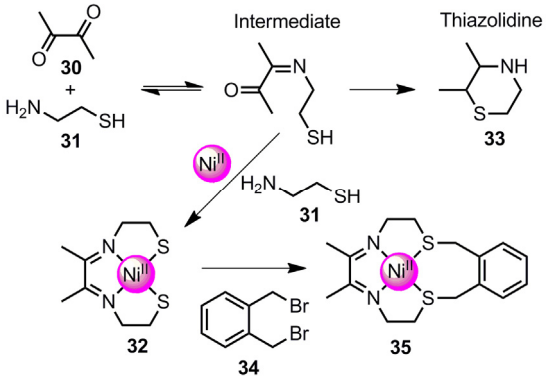
1.4.2 Passive Transition Metal Templates

In the 1960s, Busch was the first to recognize the potential of a metal ion to direct organic reactions.[44] The key features of this newly discovered metal template effect were identified as being:[45] (a) *ligand stabilization/activation* — formation of a metal–ligand complex can either protect a given ligand or, conversely, activate it towards further reaction; (b) *ligand orientation* — the preferred coordination geometry of a metal ion is a source of 'geometric information'[46] that is to say that a metal ion can 'gather' ligands in a well defined and often predictable geometry; c) *effective concentration of the coordinated ligands* — the metal template can bring building blocks together so that their proximity results in the increased probability of reaction between ligands in the same coordination sphere.

The first application of this template effect to macrocycle synthesis was reported by Busch in 1964.[47] A Ni^{II} template sequestered diimine **32** from an equilibrium mixture in the reaction of α-diketone **30** with β-mercaptoethylamine **31** in preference to by-

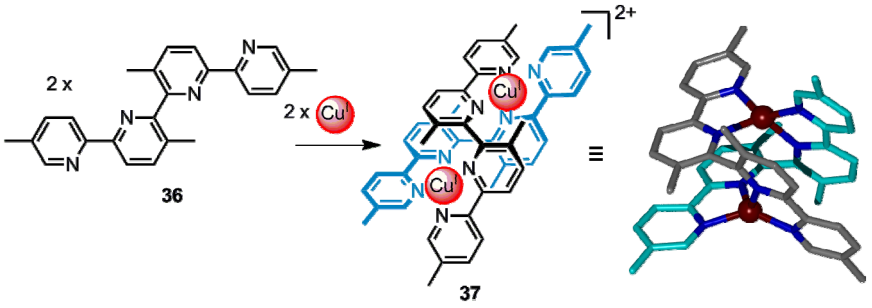
product **33**, an example of a thermodynamic template effect (Scheme 1.11). This Schiff base **32** could then undergo reaction with α,α'-dibromoxylene **34** to afford the macrocyclic complex **35** rather than oligomeric by-products, exemplifying a kinetic template effect.

Scheme 1.11. The first template directed macrocycle synthesis.



Further developments in the field—crown ether synthesis by Pederson, synthesis[48] and study[49] of cryptands by Lehn and Cram—led to award of the 1987 Nobel Prize in Chemistry for the *"development and use of molecules with structure-specific interactions of high selectivity."* The concepts of self-recognition and molecular self assembly that underpinned these early investigations now permeate through many diverse areas of science. In terms of chemical templation, these ideas were applied to the synthesis of more elaborate structures; one notable example is Lehn's use of Cu^{I} ions to assemble 'helicates' (Scheme 1.12).[50] Due to the limited flexibility of the quaterpyridyl ligands used and the geometrical constraints imposed upon them by tetrahedral Cu^{I} ions a helical–bimetallic complex was obtained.

Scheme 1.12. Lehn's assembly of a dinuclear Cu^{I} helicate.

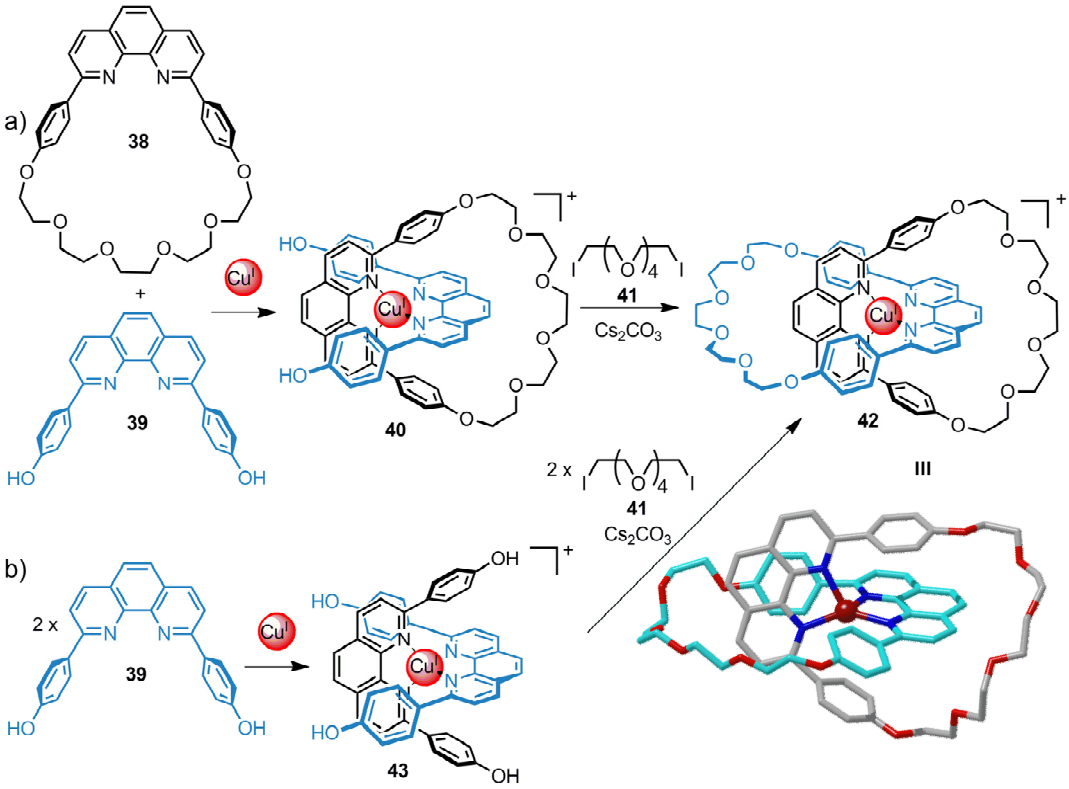


1.4.2.1 The Sauvage Revolution – Tetrahedral Metal Templates

In the early 1980s, the huge potential of chemical templates for the construction of MIMs was recognized by Jean-Pierre Sauvage. He reported the first metal template assembly of a catenane in 1983, revolutionizing the synthesis of MIMs (*vide supra – Section 1.4)*.

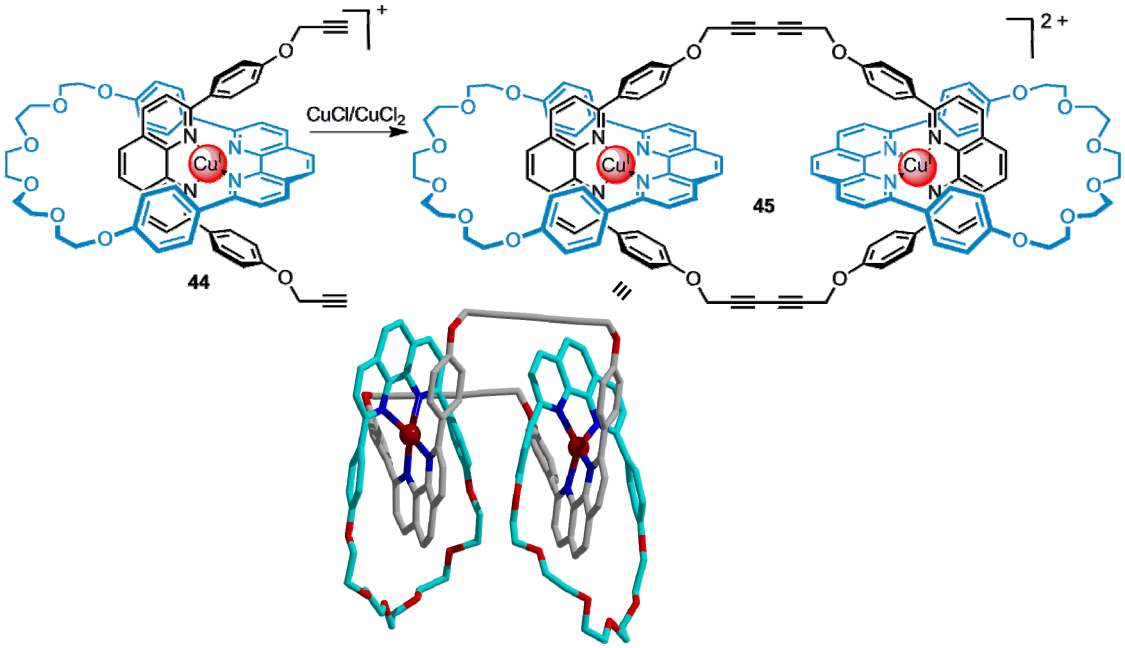
Sauvage's elegant strategy made use of the tetrahedral coordination geometry of a Cu^{I} ion to hold two 2,9-diphenyl-1,10-phenanthroline(dpp)-containing fragments orthogonally, creating a 'cross-over point'. In the first published example he described the combination of pre-formed macrocyclic dpp ligand **38** and a bishydroxyl dpp ligand **39** in a threading-followed-by-clipping strategy (Scheme 1.13a). Ring closure was performed using Williamson ether synthesis affording the target catenane **42** in 42% yield. In addition to the single macrocyclization approach, the following year Sauvage went on to show that double macrocyclization of the homoleptic complex **43**—formed quantitatively from two equivalent of dpp ligand **39** and one equivalent of Cu^{I}—could be achieved in 27% (Scheme 1.13b). The metal-complexed catenane (or *catenate*) could be demetallated with KCN to give the metal-free *catenand,* although the rate at which the demetallation proceeded was found to be several orders of magnitude slower than that for analogous non-interlocked dpp complexes.[51] The exceptionally high stability of the metal–interlocked ligand complex was termed 'the catenand effect' – an extension of the chelate, macrocycle and cryptate effects.

Scheme 1.13. Sauvage's Cu^{I} template synthesis of a [2]catenane by a) single macrocyclization and b) double macrocyclization.



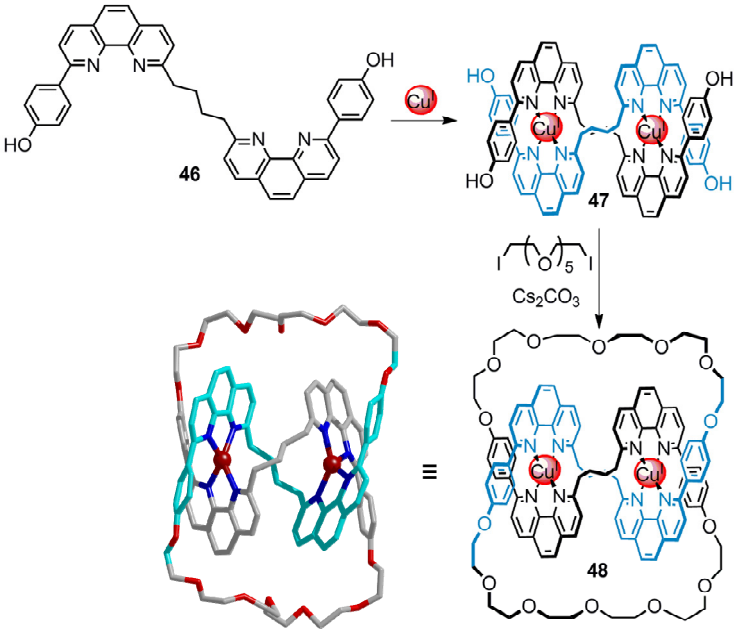
The Cu^{I}–$(dpp)_2$ motif has since been used by Sauvage and others as the central template in the synthesis of many other structures. The first metal-template synthesis of a [3]catenane, using Williamson ether macrocylizations proceeded in a rather low yield of 6%.[52] However, a later approach using Glaser–Eglington oxidative coupling of terminal acetylene groups for the macrocyclization step proceeded in a much higher 58% yield (Scheme 1.14).[53] This was an early indication that judicious choice of the method of covalent capture employed could drastically improve the efficiency of a template directed synthesis (*vide infra – Section 1.4.2.2)*. In addition to the target [3]catenane **45**, 22% of a tri-metallic complex was isolated which was proposed to be a [4]catenate.

Scheme 1.14. A [3]catenane built around the Cu^{I}–$(dpp)_2$ motif.



The effectiveness of Cu^{I}–$(dpp)_2$–type template motifs to induce cross-over points was demonstrated further when, in 1989, Sauvage reported the synthesis of the first molecular knot **48**, constructed around two Cu^{I} centers (Scheme 1.15).[54] Ligand **46** was synthesized bearing two dpp units tethered by a four-carbon-long alkyl linker, upon complexation with Cu^{I} a dinuclear helical complex **47** could form (*cf. Lehn's helicates – Section 1.4.2)*. The helical complex **47** has the three required cross-over points so that linkage of the four hydroxyl end groups by Williamson ether synthesis produced a molecular trefoil knot – the first of its kind. Unambiguous confirmation of the knotted structure was later reported in the form of the solid-state structure as determined by X-ray crystallography of a single crystal.[55] Although the synthesis of the first molecular knot was a great achievement, trefoil **48** was isolated in a yield of only 3% due to the poor efficiency of helix formation – the flexible four-carbon-long alkyl linker allowed the ligand to fold around to form a more stable mononuclear complex. Subsequent improvements to the yield were made by employing a rigid aryl linker in place of the alkyl chain[56] and by linking the ends of the helicate by RCM instead of a Williamson ether synthesis.[57]

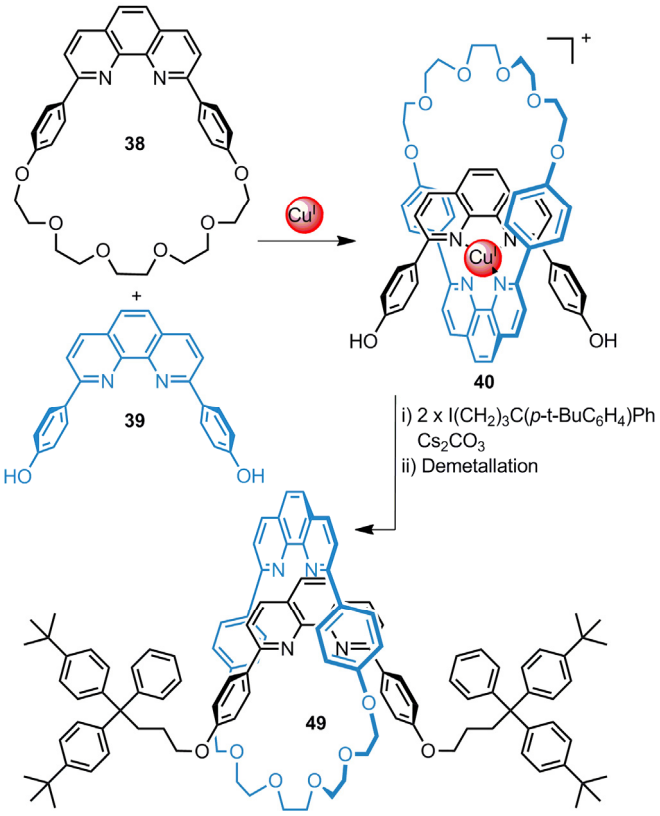
Scheme 1.15. The first synthesis of a molecular trefoil knot.



Somewhat surprisingly the synthesis of a rotaxane via a metal templated assembly process was not reported until 1991 (Scheme 1.16)[58] – eight years after Sauvage's first catenane and after the technique had been applied to the more challenging synthesis of a trefoil knot. Gibson, using the same heteroleptic complex **40** which had been an intermediate in the single macrocyclization catenane synthesis (Scheme 1.13a), introduced stoppering groups via Williamson ether synthesis to produce the rotaxane. Demetallation by ion-exchange with an Amberlite–CN resin afforded the metal free MIM **49** in 42% yield (Scheme 1.16).

The tetrahedral Cu^{I} ion has proven to be an excellent source of geometric information with which to induce a cross-over point between two bidentate ligands—particularly dpp ligands—for the construction of MIMs. However there are of course a rich variety of metal ions with varied coordination spheres that can be exploited to bring together molecular building blocks and create cross-over points. Metal ions with all the simple coordination geometries (coordination number ≤ 6) have been utilized in the construction of MIMs. In the following sections the means of covalent capture will be discussed briefly before discourse on the commonly employed coordination geometries.

Scheme 1.16. Gibson's metal template synthesis of a [2]rotaxane.



1.4.2.2 Methods of Covalent Capture

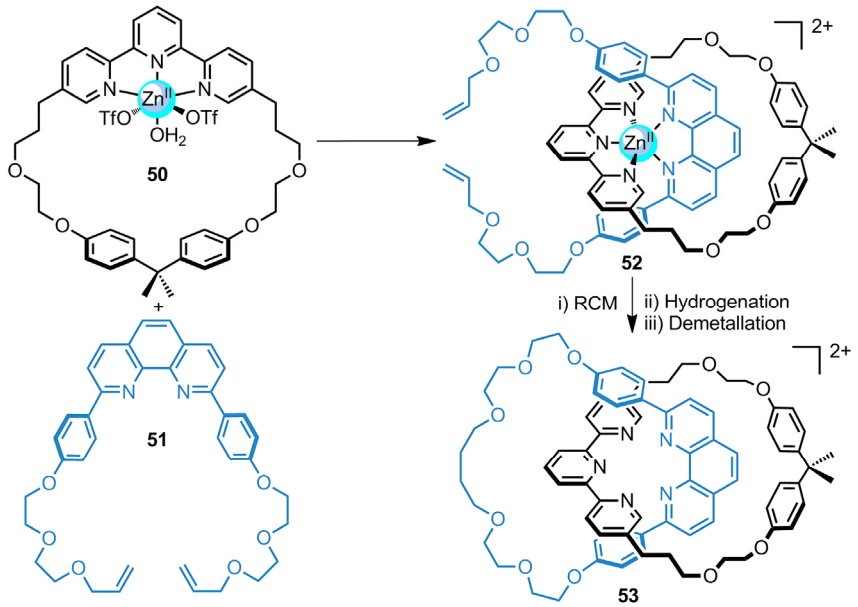
After a metal ion has gathered ligands into the desired geometry—designed to promote interlocking—a suitable means of covalent bond formation must be employed to trap the MIM. In the case of many of the early metal template syntheses of MIMs the role was fulfilled by Williamson ether synthesis[59] or, for large macrocycle formation especially, Glaser–Eglington acetylenic coupling.[60] More recently, imine bond formation[61] has been used effectively as a high yielding, mild bond forming step with the one caveat that the desired product must be thermodynamically favored. The recent advent of two highly efficient and mild reactions, ring-closing olefin metathesis[62] (RCM) and the Huisgen–Meldal–Fokin Cu^{I}-catalyzed 1,3-cycloaddition of terminal alkynes with azides[63] (the CuAAC 'click' reaction), has led to considerably increased yields in many syntheses of MIMs. The effectiveness of these reactions can be explained by their high functional group specificity, the high stability of the reactive end groups and because the reactions are

often carried out under conditions, non-polar solvents at room temperature, which do not disrupt favorable secondary non-covalent interactions.

1.4.2.3 Trigonal Bipyramidal Metal Templates

Although there are a number examples of rotaxanes and catenanes bearing trigonal bipyramidal binding sites, these are often systems with more than one binding site that have been constructed around a tetrahedral template (*vide supra – Section 1.4.2.1*) such as Sauvage's 'redox switchable catenane'.[64] On one of the rare occasions in which a trigonal bipyramidal template has been used in the construction of a MIM, Sauvage employed a Zn^{II} ion capable of adopting 4, 5 or 6 coordinate complexes and a combination of tridentate and bidentate ligands (Scheme 1.17).[65] Covalent capture of the heteroleptic complex **52** was achieved using RCM followed by hydrogenation of the resulting mixture of *cis/trans*–cyclic olefins. Demetallation by a basic, aqueous work up afforded the metal free catenane in a 40% yield.

Scheme 1.17. Catenane synthesis using a trigonal bipyramidal coordination geometry.



1.4.2.4 Octahedral Metal Templates

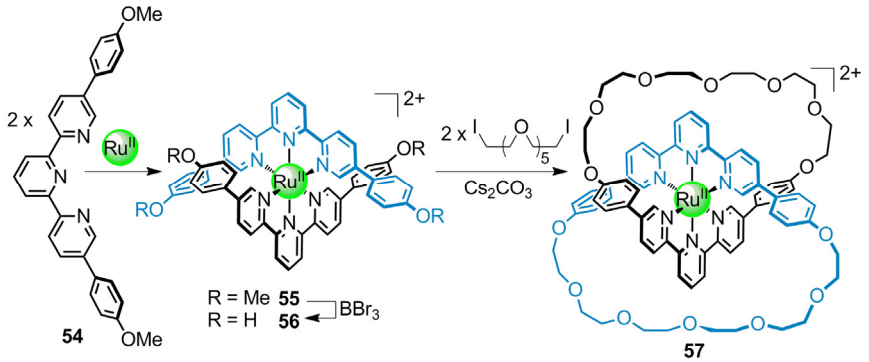
The octahedral coordination geometry offers three potential combinations of ligands which are suitable for creating cross-over points. The "3+3" ligand set—a

combination of two tridentate ligands—was the obvious first choice given its evident predisposition to hold the two ligands orthogonally in a manner similar to the "2+2" tetrahedral geometry. Two alternative ligand sets have also been explored, the "4+2" strategy using one tetradentate ligand and another bidentate ligand to create the crossing point or, more recently, a "2+2+2" strategy to entwine three bidentate ligands.

A) "3+3" LIGAND SETS

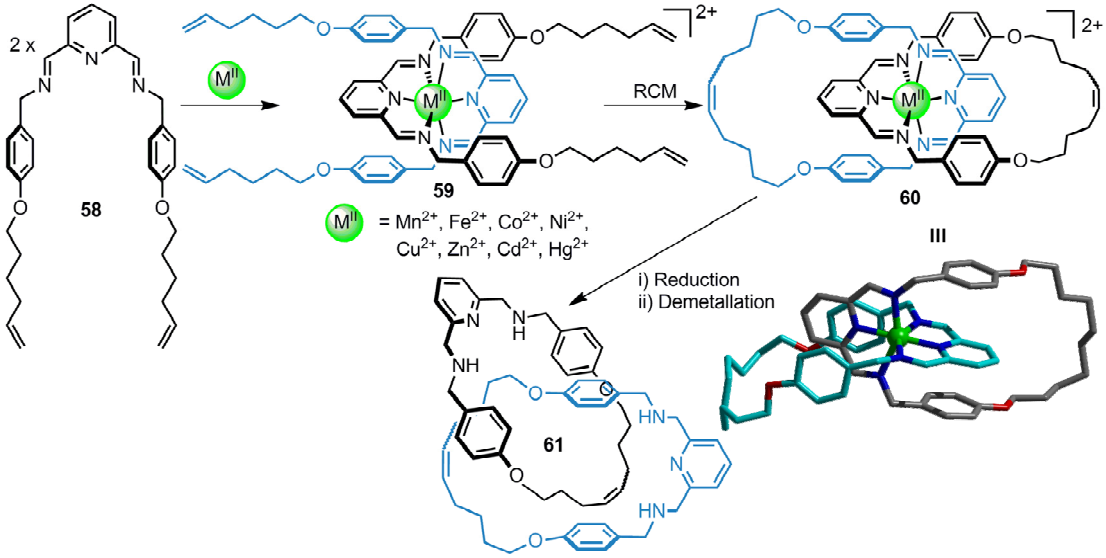
In 1991 Sauvage yet again cemented his position at the forefront of template synthesis – he reported the first octahedral metal template used in the assembly of a MIM[66] which involved the use of a tridentate 5,5"-diphenyl-terpyridine ligand in the construction of catenate complex **57** from **56** using a "3+3" approach (Scheme 1.18). The Ru^{II} ion held the two tridentate ligands orthogonally during a Williamson alkylation reaction to afford catenate **57** in a modest 11% yield which, due to the catenand effect (*vide supra – Section 1.4.2.1*) and steric crowding in addition to the high kinetic stability of Ru^{II}, could not be demetallated to the free catenane. Attempts to improve upon the modest yield through use of RCM proved unsuccessful, yielding a 'figure-of-8' complex, formed by inter-ligand metathesis, instead of interlocked rings.[67] Sauvage had relatively more success applying the "3+3" terpyridine motif to the synthesis of a trefoil knot in a 20% yield, applying the same tactics as he had done previously to create two cross-over points via a bimetallic Fe^{II} helicate.[68]

Scheme 1.18. Sauvage's synthesis of a Ru^{II}–catenate.



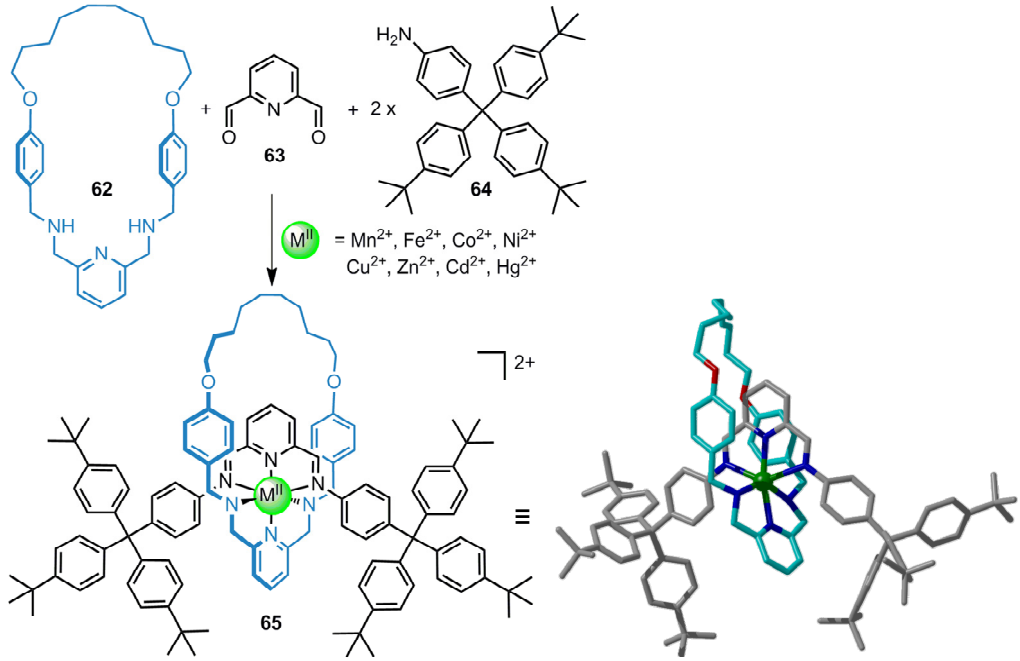
The problems encountered by Sauvage and others[69] employing similar ligand sets were in part due to the rather low turn angle (~60°) of the ligands, resulting in increased probability of inter-ligand couplings. Leigh and co-workers reported the use of a 2,6-diiminopyridine coordination motif with a 180° turn angle in combination with various divalent octahedral metal ions and covalent capture by RCM to access catenanes in high yields of up to 81% (Scheme 1.19).[70]

Scheme 1.19. Leigh's combination of an octahedral template with 180° turn ligands.



As an alternative to the catenane formation under kinetic conditions (RCM), Leigh also reported a similar process under thermodynamic control – using reversible imine formation as the macrocyclization step, creating the 2,6-diiminopyridine coordination motif *in situ*. By using a preformed bisamine macrocycle **62** and forming a 2,6-diiminopyridine dumbbell reversibly under thermodynamic control, rotaxanes **65** could be synthesised in near quantitative yields (Scheme 1.20).[71] Recently a 'harder' metal ion was used as the template; the octahedral trivalent Co^{III} ion was used in the assembly of both a catenane and a rotaxane.[72]

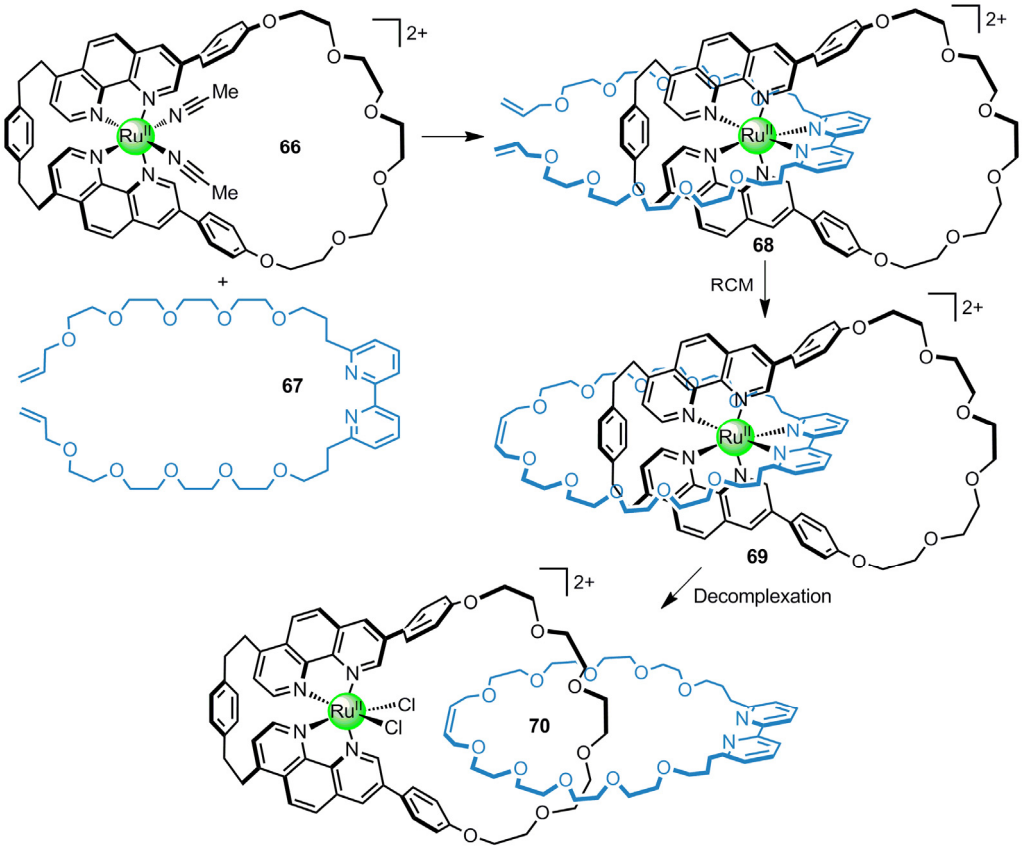
Scheme 1.20. [2]Rotaxane synthesis around an octahedral metal ion via reversible imine formation.



B) "4+2" LIGAND SETS

In 2003 Sauvage reported covalent capture of catenane **69** in a 68% yield from heteroleptic octahedral Ru^{II} complex **68** composed of tetradentate bisphenanthroline macrocycle **66** and bidentate macrocycle precursor **68**.[73] This represented the first time that a "4+2" ligand set had been successfully used to construct a MIM. Photo-induced dissociation of the bipyridyl ligand in the presence of chloride ions generated catenane **70** in which the rings could rotate freely relative to one another. In addition to this single macrocyclization pathway to [2]catenanes, a double macrocyclization approach was shown to be viable and the ligand set was also used effectively to synthesize [2]rotaxanes.[74]

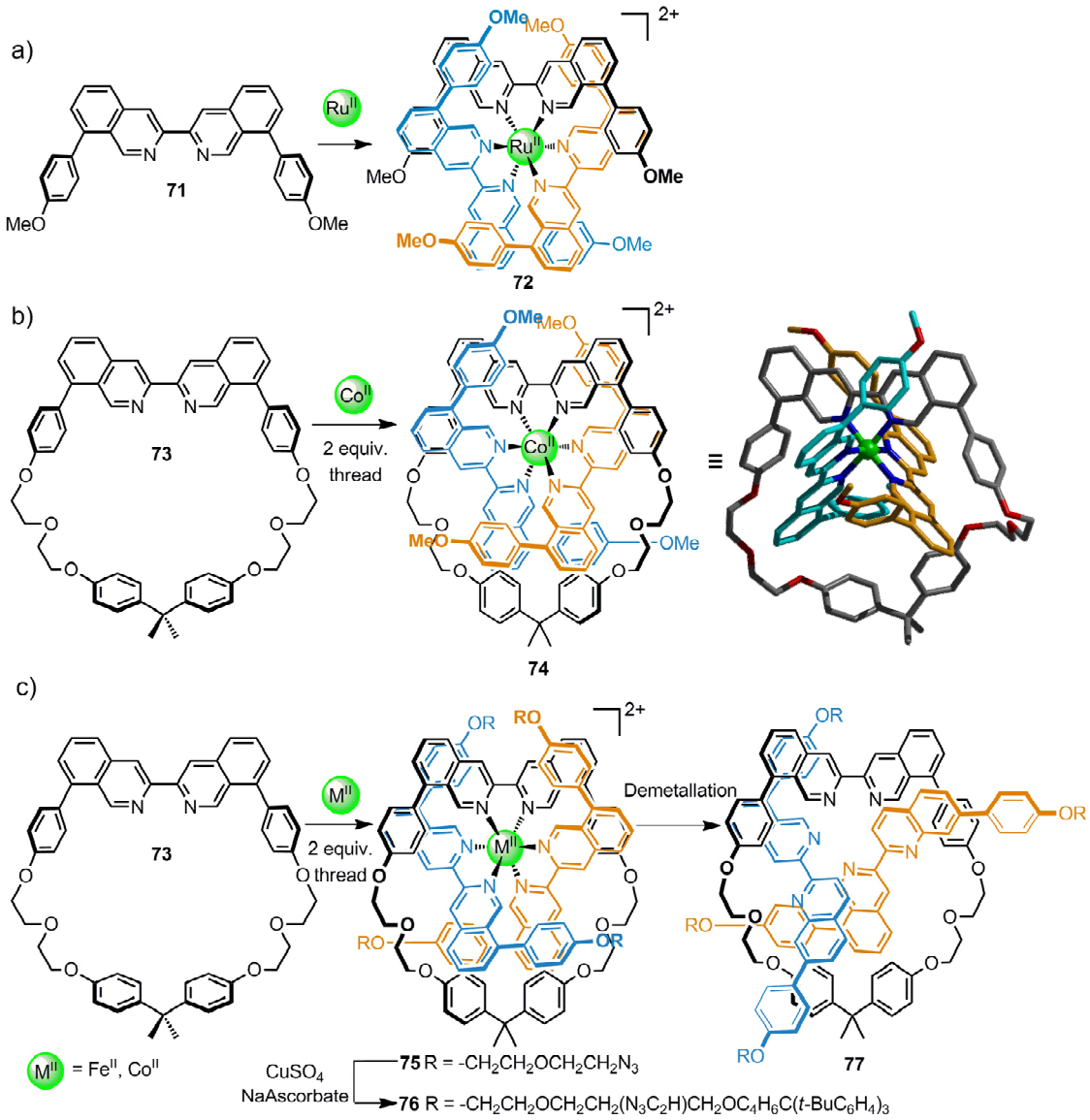
Scheme 1.21. Sauvage's use of a "4+2" ligand set for the assembly of a catenane.



C) "2+2+2" LIGAND SETS

After successfully implementing a "4+2" ligand set, Sauvage directed his attention toward a "2+2+2" strategy to entwine three ligands in order to synthesize a doubly threaded [3]rotaxane. Initial investigations indicated that complex formation of three standard phenanthryl or bipyridyl bidentate ligands around a Ru^{II} or Fe^{II} ion was too sterically demanding; a "2+2+2" complex could not form due to overcrowding around the metal center. A less sterically congested ligand was required and Sauvage developed larger bidentate ligand **71** with a biisoquinoline motif to fulfill this purpose.[75] The "2+2+2" ruthenium complex of ligand **71** was successfully prepared (Scheme 1.22a) and X-ray crystallographic evidence showed [3]pseudorotaxane **74** could be prepared from macrocycle **73** with a Co^{II} center and two equivalents of ligand **71** (Scheme 1.22b).[76]

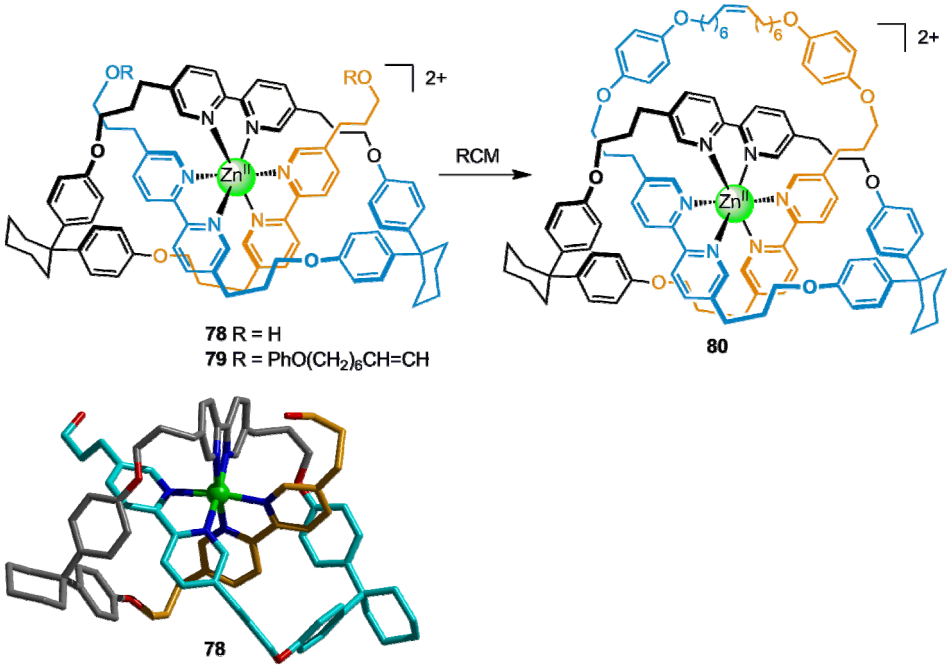
Scheme 1.22. Spacious biisoquinoline ligands **71** and **73** and a,b) their "2+2+2" complexes c) application in threading-followed-by-stoppering [3]rotaxane synthesis.



Two azide terminated biisoquinoline axles could be threaded through macrocycle **73** and the [3]pseudorotaxane complex **75** stoppered via a CuAAC reaction to give **76** in up to 94% (Scheme 1.22c).[77] Demetallation with KCN could only be achieved for the Co^{II} complex of **76** to afford the free [3]rotaxane **77**. However the cavity size of the macrocyclic component was sufficiently large to 'slip' over the stoppering groups leading to gradual dissociation of the thread components at room temperature.

Hunter and co-workers reported the 'open knot' structure **78** which spontaneously formed when a ligand bearing three bipyridyl moieties was complexed with an octahedral metal ion (Scheme 1.23).[78] The "2+2+2" arrangement of the ligand around the central metal ion caused the linear ligand to 'wrap up' into a conformation with three cross-over points. In 2010, Hunter reported that linking terminal olefin end groups using RCM, completing the elegant synthesis of trefoil knot **80**.[79]

Scheme 1.23. Hunter's octahedral metal template synthesis of a trefoil knot.

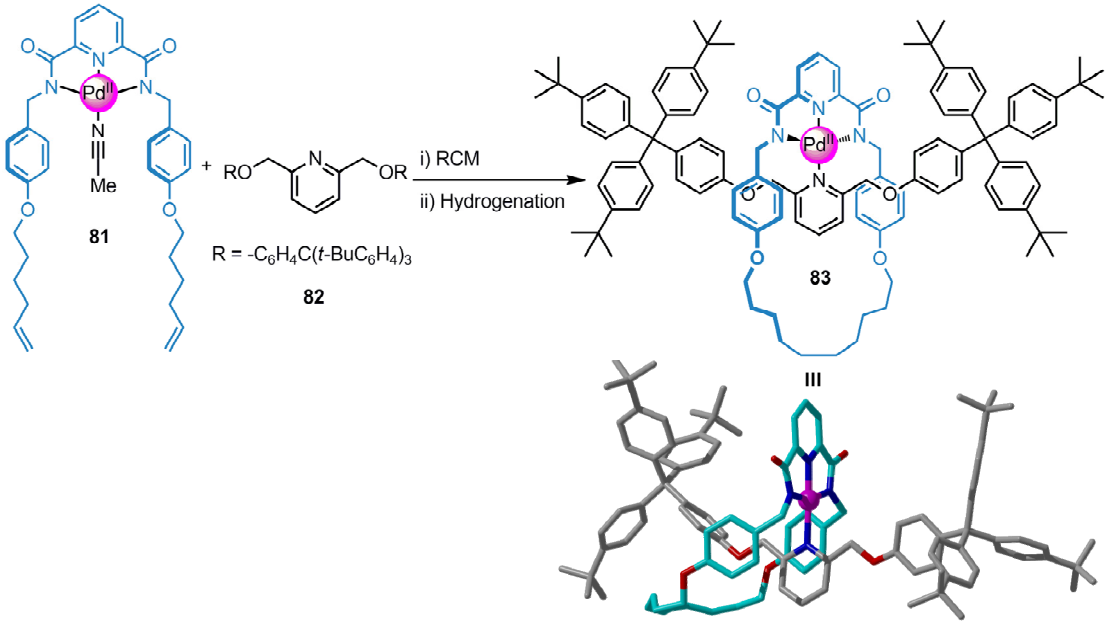


1.4.2.5 Square Planar Metal Templates

Intuitively, 2-dimensional square planar coordination geometry does not lend itself to creating a cross-over point as easily as the tetrahedral or octahedral geometries; a "2+2" ligand arrangement would not be held orthogonally and would likely be disfavored on steric grounds. However, Sauvage demonstrated that a "3+1" ligand set could create a cross-over point in 2003 when he reported pseudorotaxane formation around a Pd^{II} ion.[80] The following year Leigh reported the application of a square planar Pd^{II} complex to the synthesis of a rotaxane **83**; a pre-rotaxane complex formed between monodentate 2,6-substituted pyridine-based dumbbell **82** and tridentate

pyridine-2,6-dicarboxamide-based macrocycle precursor **81** was trapped by RCM in a 77% yield (Scheme 1.24).[81]

Scheme 1.24. Leigh's square planar metal template synthesis of a [2]rotaxane.



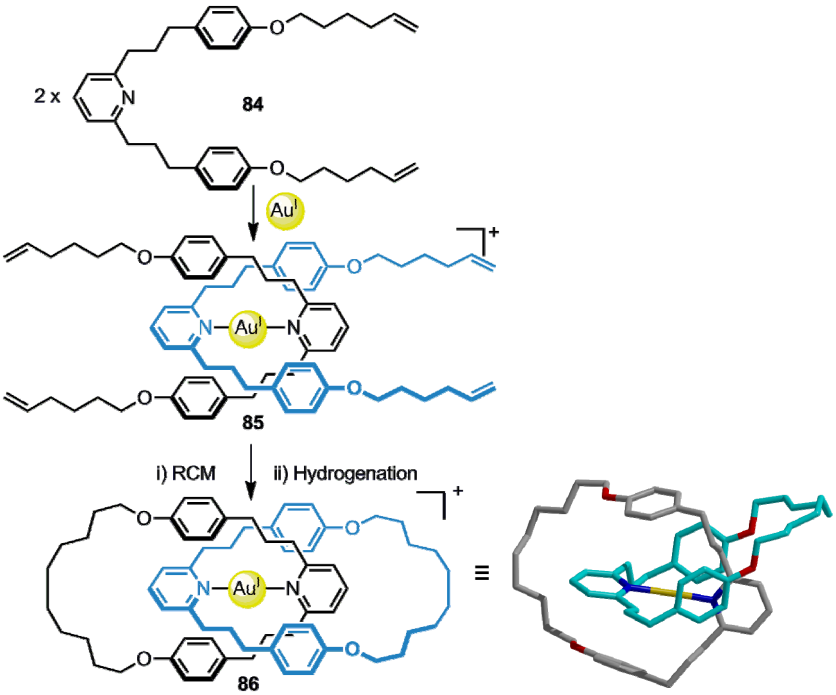
The high efficiency of this process allowed Leigh to add up to three rings sequentially to a longer axle by iterative complexation, RCM and demetallation.[82] When interlocking a number of different macrocycles, the order in which these rings were introduced was exploited to demonstrate the principles of sequence isomerism in [3]rotaxanes.[83] Takata and Hirano demonstrated the use of a similar "3+1" ligand set in a threading-followed-by-stoppering [2]rotaxane synthesis[84] and Leigh went on to demonstrate the application of the square planar geometry to catenane synthesis.[85]

1.4.2.6 Linear Metal Templates

The last of the coordination geometries (with a coordination number ≤ 6) to be employed in the construction of a MIM was the linear geometry. The reason behind its late introduction is the obvious challenge in exploiting a 1-dimensional template to gather ligands in a well defined manner in 3-dimensional space. Leigh and co-workers successfully used the preferred linear coordination geometry of Au^{I} in combination with other secondary non-covalent interactions to create a cross-over

point between two monodentate ligands.[86] Two 2,6-disubstituted pyridine ligands were used in either a double macrocyclization synthesis of a [2]catenane **86** (Scheme 1.25) or a clipping synthesis of a rotaxane.

Scheme 1.25. Au^{I} templated clipping assembly of a [2]catenane.



1.4.3 Active Metal Templates

1.*4.3.1 The Active Metal Template Concept*

In the previous section a variety of transition metal ions were shown to function as a sort of 'molecular glue' in what can be termed a 'passive template' strategy; they hold the components together in space prior to a covalent bond forming step to trap the MIM. The metal ions used for this purpose include Cu^{I}, Pd^{II}, Ni^{II}, Ru^{II} and others that are also well known to act as efficient homogeneous catalysts given the correct ligand system and substrates. In 2006 Leigh and co-workers reported the first example of an 'active metal template' (AMT) reaction in which the catalytic activity of a metal ion was exploited in unison with its template effect to construct a MIM.[87] The name—

active metal template—derives from the fact that the metal ion is not passive in the covalent bond forming step, rather it actively mediates this process in addition to its role as the chemical template.

The cornerstone of this approach is that the metal ion is bound endotopically within the macrocycle cavity.[88] Coordination of two stoppered 'half-threads' to the metal ion—immobilized within the ring—then occurs from either face of the macrocycle, partly due to the coordination geometry of the metal and partly as a result of the steric repulsion between the two bulky stoppering groups (Figure 1.4). Metal-mediated covalent bond formation between the 'half-threads' then proceeds *through* the ring as a result of these geometric constraints, simultaneously creating a new mechanical bond.

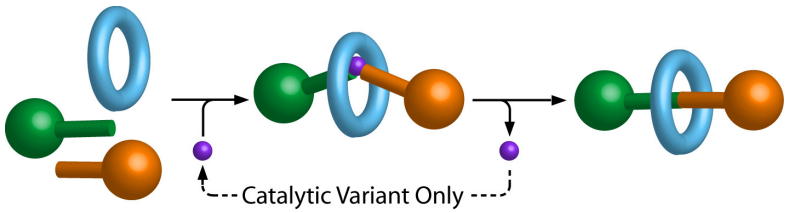


Figure 1.4. Schematic representation of the AMT strategy – a metal ion (purple) bound within the cavity of a macrocycle (blue) mediates bond formation between two 'half-threads' (green and orange) *through* the ring to assemble a [2]rotaxane. In some cases the metal can turn over (dashed arrow), acting as a catalytic template.

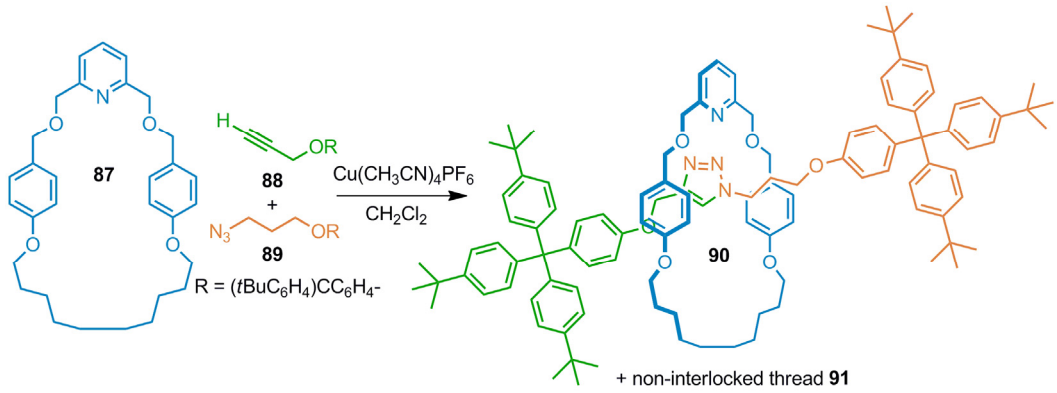
The AMT strategy has several features which are potentially attractive when considering the synthesis of MIMs: (a) *high efficiency* — the components of the MIM are gathered and covalently trapped simultaneously in contrast to the two-step passive metal template assembly; in addition, if the metal ion can dissociate from the rotaxane under the reaction conditions the metal template may be able to be used in sub-stoichiometric quantities; (b) *structural diversity* — a latent metal binding site remains on the macrocycle however other recognition sites are not required in contrast to all other template approaches in which all interlocked component bear permanent template sites, the design of the interlocked structure is therefore less restricted by the means of its assembly; (c) *versatility* — the general AMT strategy can, in theory, be applied to many of the well established metal mediated bond

forming reactions and additionally organocatalytic reactions are potentially compatible; (d) *topology* — other types of interlocked structures other than simple [2]rotaxanes could also be accessed using the AMT strategy and; finally, (e) *reaction mechanism elucidation* — the unique interlocked nature of the intermediates during key stages the AMT transformation can provide mechanistic insight into the catalytic process that would not be obtainable otherwise.

1.4.3.2 CuAAC Active Metal Template

The first reported AMT reaction[89] made use of the Huisgen–Meldal–Fokin Cu^{I}-catalyzed 1,3-cycloaddition of terminal alkynes with azides (the CuAAC 'click' reaction). The CuAAC reaction was an ideal candidate for initial investigations of the AMT concept owing to the mild reactions conditions, associated high yields, the stability of alkyne and azide functional groups and the dramatic rate acceleration (>10^7) induced by Cu^{I} catalysis. Crucially, in organic solvents, the reaction kinetics of the CuAAC reactions are enhanced by tertiary amines or pyridines.[90]

Scheme 1.26. The first AMT reaction, a CuAAC 'click' reaction occurs in the cavity of macrocycle **87**.



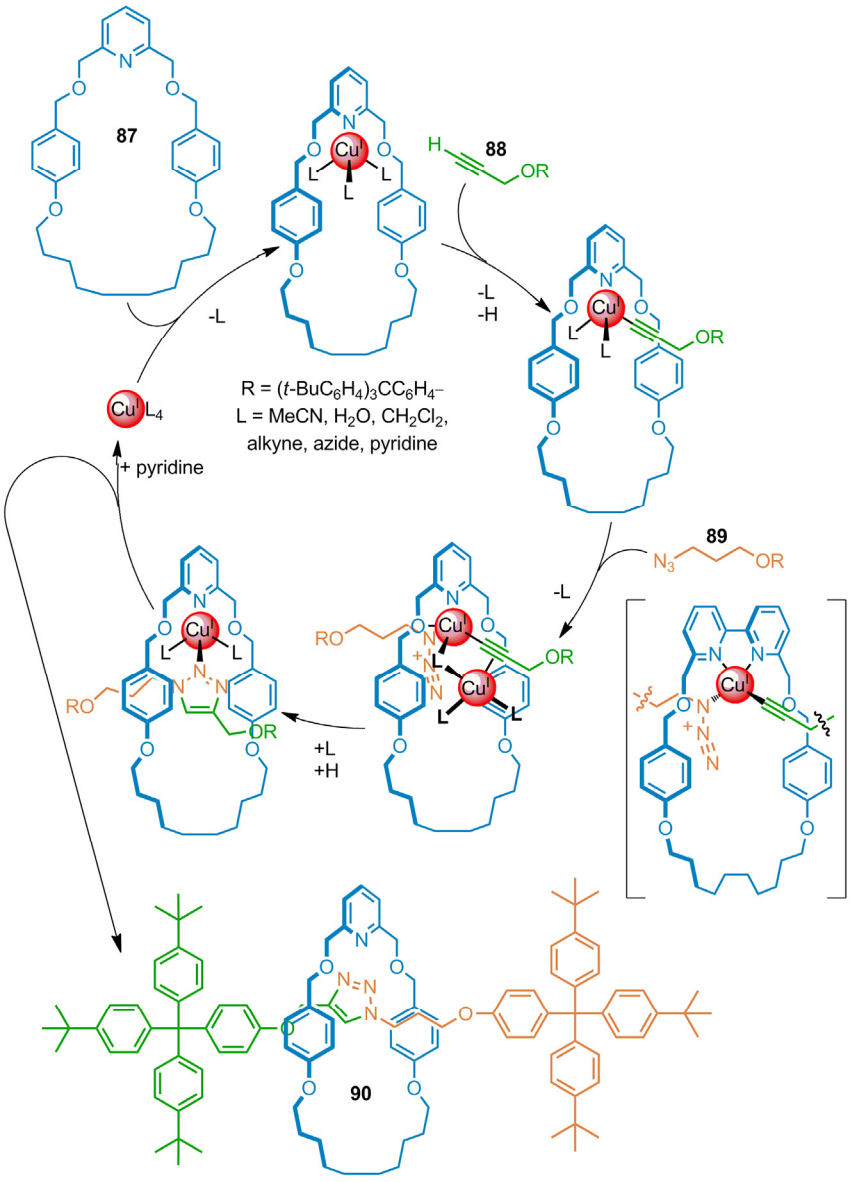
Taking the features of the CuAAC reaction into account, Leigh and co-workers employed macrocycle **87** bearing an endotopic pyridine binding site to sequester Cu^{I} ions within its cavity and alkyne and azide 'half-threads' (**88** and **89** respectively). Overnight stirring of equimolar amounts of these reagents with one equivalent of $[Cu(CH_3CN)_4]PF_6$, an organic solvent soluble source of Cu^{I} ions, in dichloromethane

at room temperature furnished [2]rotaxane **90** (57%) and non-interlocked thread **91** (41%) after demetallation with KCN (Scheme 1.26).

When using a stoichiometric quantity of the Cu^{I} catalyst, yields of up to 94% of [2]rotaxane **90** with respect to macrocycle **87** could be isolated simply by using an excess of alkyne **88** and azide **89**. Preliminary attempts to employ only a catalytic quantity of metal ion where hindered as the product **90** appeared to sequester the Cu^{I} and inhibit further catalytic activity i.e. when 20 mol% of $[Cu(CH_3CN)_4]PF_6$ was used a maximum of 20% of [2]rotaxane **90** could be recovered. Addition of pyridine as a competing ligand allowed the catalyst to turn over, presumably by facilitating the extraction of the Cu^{I} from the product [2]rotaxane **90**. Under the optimized sub-stoichiometric conditions, 82% of [2]rotaxane was generated using 20 mol% of catalyst – the first time a catalytic amount of template had been used to assemble a MIM.

A systematic investigation of the reaction parameters and constitution of the macrocyclic component provided insight into the requirements of the CuAAC AMT reaction. It was determined that the presence of either one or two strongly coordinating endotopic donor atoms on the macrocycle was essential; a tridentate analogue failed to produce rotaxane as did macrocycles lacking good binding sites. Kinetic studies indicated that, although the CuAAC reaction occurred more rapidly in the absence of a macrocyclic ligand, the excellent coordinating ability of the macrocycle means it can essentially sequester the majority of the Cu^{I}, favoring rotaxane formation as a result. The observation that the rate of formation of thread *and* [2]rotaxane was increased in the presence of two equivalents of Cu^{I} provided some evidence that the CuAAC reaction was proceeding via a bimetallic intermediate. Further evidence in the form of the unexpectedly high yield of [3]rotaxane under certain conditions (*vide infra – Section 1.4.3.7*) supported this notion and the authors proposed the mechanism for the productive [2]rotaxane forming pathway shown in Scheme 1.27.

Scheme 1.27. Mechanism of the catalytic 'click' AMT reaction.

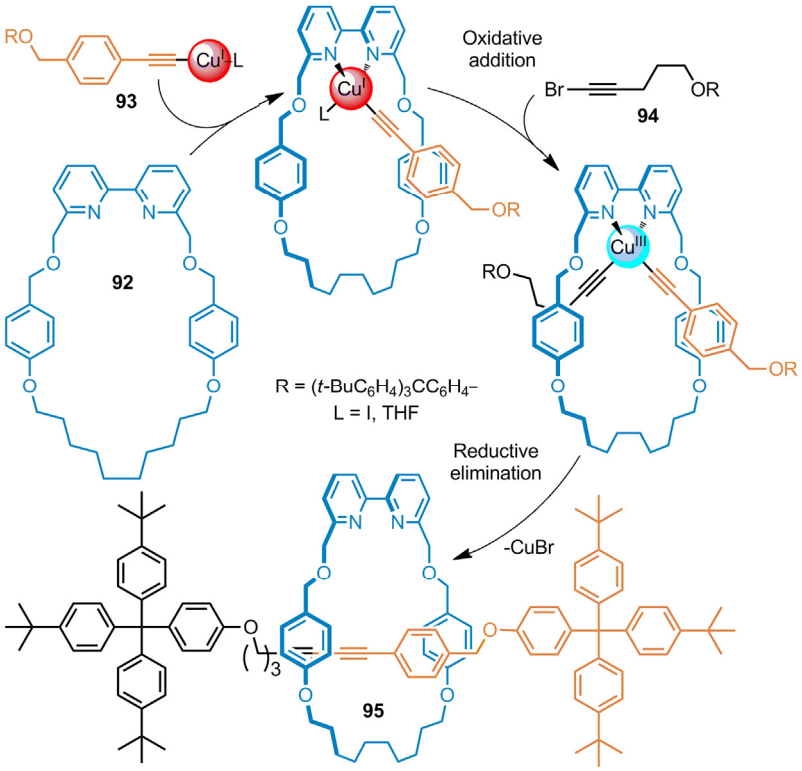


1.4.3.3 Other Cu-based AMT Reactions

Following on from the development of the 'click' AMT reaction, Leigh and co-workers investigated a number of different transition metal catalyzed processes. One such example which also made use of a Cu^{I} heterocoupling was based on the Cadiot–Chodkiewicz reaction (Scheme1.28).[91] A preformed alkynyl cuprate **93** was mixed with bipyridyl macrocycle **92** prior to addition of the alkynyl halide coupling partner

94 giving high yields (up to 85%) of [2]rotaxane with excellent selectivity for hetero- versus homocoupled product (>95%).

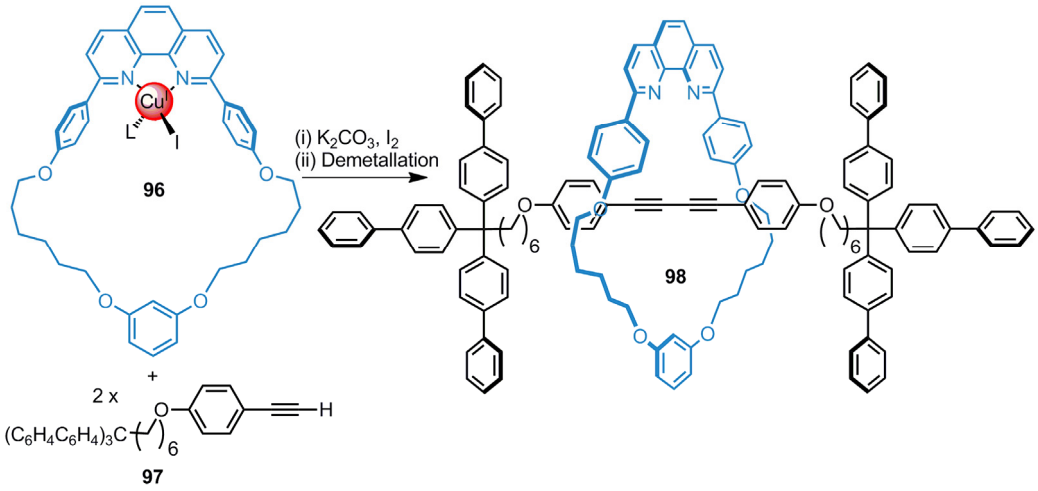
Scheme 1.28. AMT Cadiot–Chodkiewicz heterocoupling mediated by Cu^{I}.



Saito and co-workers reported the application of the classic Cu^{I}(dpp) motif in an AMT strategy using either an Ullman-type thioether synthesis and an oxidative alkyne homocoupling (Glaser coupling).[92] One molar equivalent of Cu^{I}–macrocycle complex **96** catalyzed C–S bond formation between ten molar equivalents of stoppered aryl iodide and a stoppered thiol producing 27% of [2]rotaxane based on **96** and large amounts non-interlocked thread. The AMT Glaser coupling reported in the same publication afforded a higher yield of [2]rotaxane **98** (72%) and better selectivity versus thread using only a small excess of stoppered alkyne **97** (Scheme 1.29). Metal-catalyzed alkyne homocoupling reactions have proven popular AMT reactions with two other separate examples reported since Saito's initial Glaser reaction (*vide infra – Section 1.4.3.4*); this is in part due to their high yielding nature

but also because they can potentially lead to rotaxanes with conjugated, rigid axles which are of interest for their structural and electronic properties.

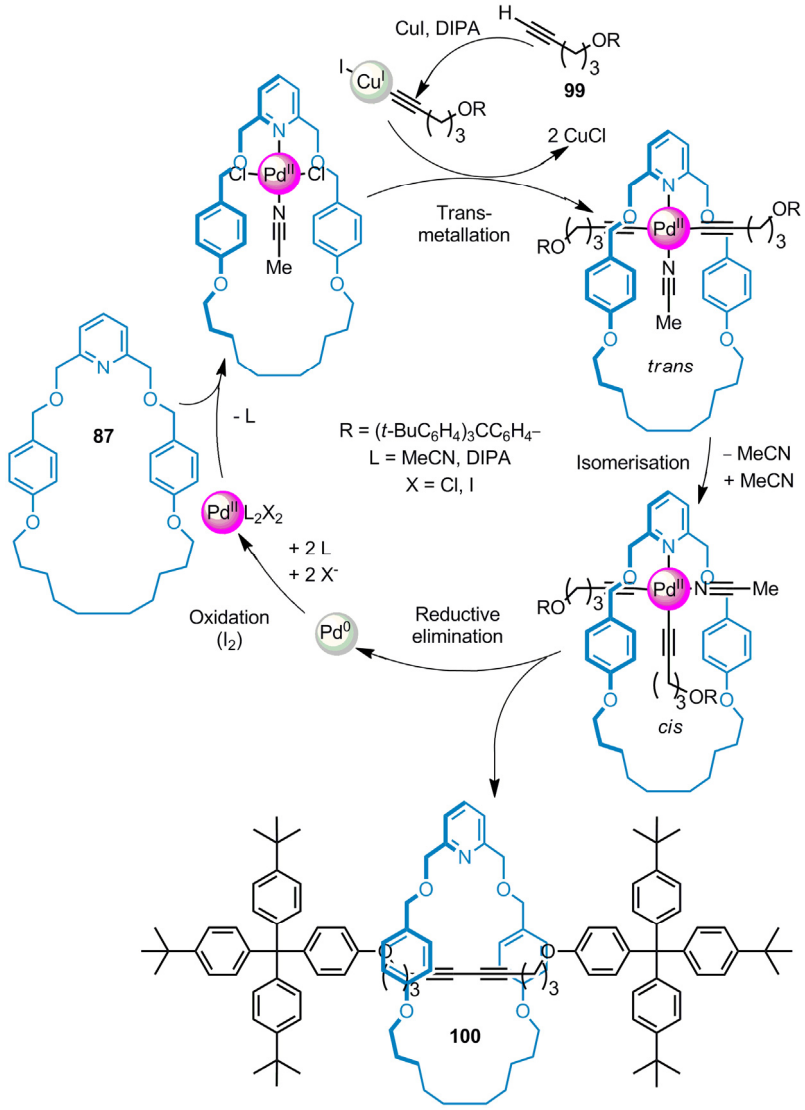
Scheme 1.29. Saito's AMT Glaser homocoupling.



1.4.3.4 Pd and Ni Acetylenic Homocouplings

In the first AMT reaction to exploit a transition metal ion other than Cu^{I}, Leigh et al. reported the use of a catalytic quantity of Pd^{II} in an alkyne dimerization reaction (Scheme 1.30).[93] X-ray crystallographic analysis of a Pd^{II} catenate similar to the Pd^{II} complex of macrocyclic ligand **87** revealed that the *trans*-coordinated chloride ligands project out of each face of the macrocycle. It was reasoned that if the chloride ligands were substituted with stoppered acetylides **99** via transmetallation the resulting threaded complex could undergo cis–trans isomerization followed by reductive elimination to produce rotaxane **100**. Indeed, under optimized conditions, with I_2 and O_2 to oxidize Pd^{II} to Pd^{0} *in situ*, 5 mol% of Pd^{II} afforded up to 90% of rotaxane **100**.

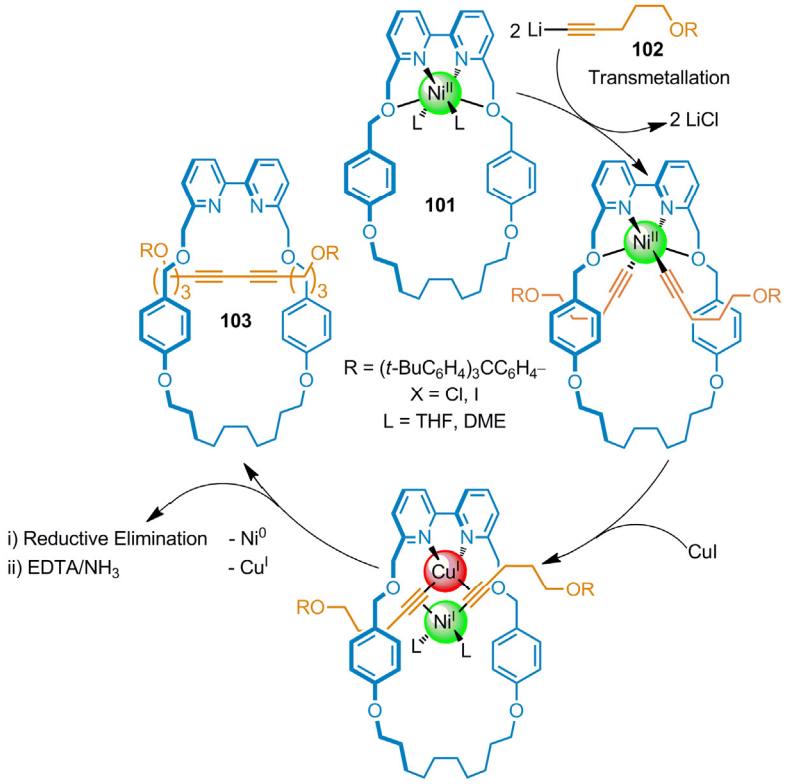
Scheme 1.30. A Pd^{II}-catalyzed homocoupling of stoppered terminal alkynes.



Further investigations showed that bipyridyl macrocycle **92** was considerably less efficient than pyridyl macrocycle **87** in the AMT Pd^{II}-catalyzed homocoupling of alkynes. Crystallographic analysis of the solid state structure of **92.PdCl$_2$** suggested this was because the square planar Pd^{II} center forced the chloride ions to protrude from the same face of the macrocycle in a manner not conducive to threading. In an effort to overcome this problem and to find a more efficient means of AMT alkyne homocoupling, Leigh and co-workers probed the use of an octahedral Ni^{II} center to mediate 1,4-diyne formation. Following extensive optimization of the reaction procedure they arrived at the most efficient AMT alkyl homocoupling reaction to date

(Scheme 1.31) which did not simply involve a Ni^{II} center as initially intended but rather proceeded via a mixed Ni^{II}/Cu^{I} intermediate.[94] The mechanistic insights into the mixed-metal catalyst system gleaned from the study demonstrated that the requirements of AMT reactions can be used as a means of mechanism elucidation.

Scheme 1.31. A mixed octahedral–tetrahedral metal catalyst system employed in an efficient AMT acetylenic homocoupling.

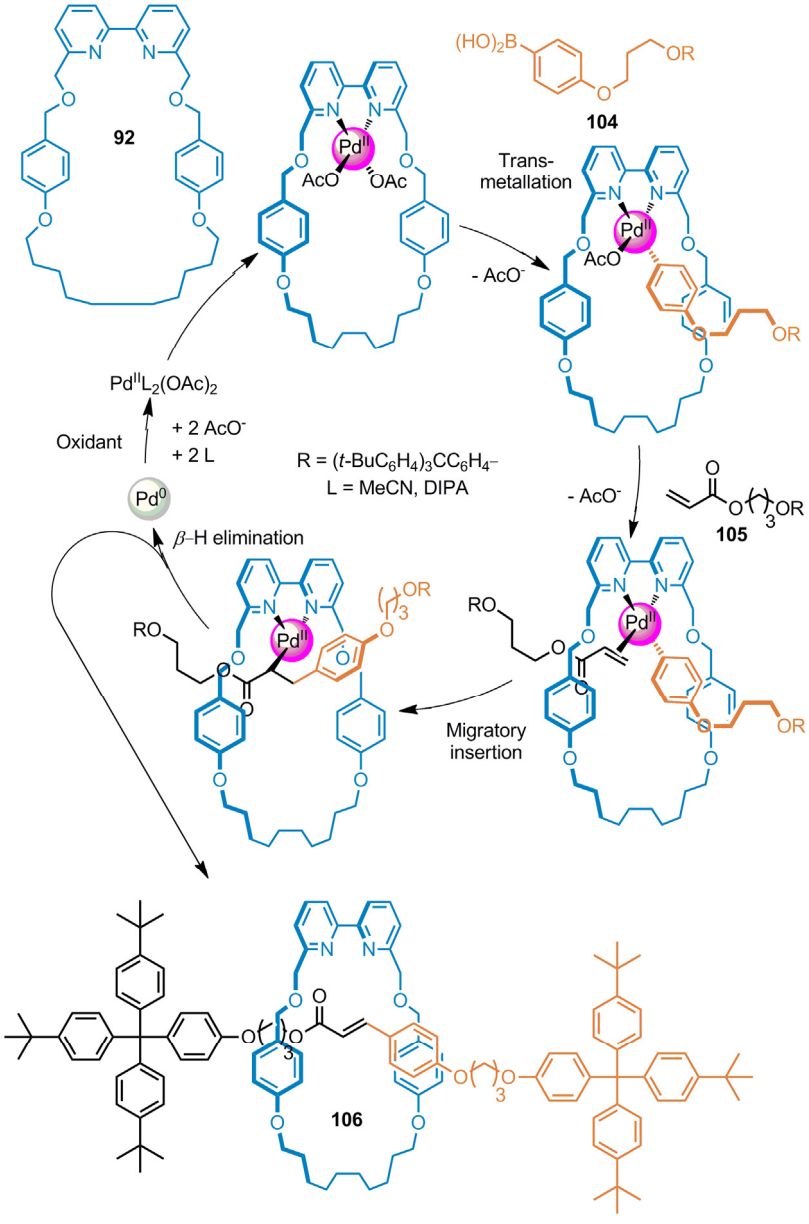


1.4.3.5 Oxidative Heck Cross Coupling

Pd^{0}-catalyzed cross coupling reactions are truly versatile and routinely high yielding and as such have become stalwart methods for connective bond forming reactions which are now ubiquitous throughout organic synthesis. An AMT Pd^{0}-catalyzed cross coupling would be a very attractive prospect, potentially transforming mechanical bond formation into a relatively simple retrosynthetic disconnection. Unfortunately, preliminary investigations by Leigh revealed that various mono-, bi- and tridentate nitrogen-donor macrocycles were unable to retain Pd^{0} to a sufficient degree to facilitate an AMT reaction, instead producing only non-interlocked products. While

simultaneously trying to design macrocycles capable of retaining Pd^0,[95] Leigh and co-workers shifted their attention to Pd^{II} oxidative Heck cross couplings as the Pd^{II} intermediates are ligated more strongly by macrocycles with nitrogen donor atoms such as **92**.[96]

Scheme 1.32. The catalytic oxidative Heck cross coupling AMT reaction.



The resulting AMT coupling of boronic acids with alkenes proved to be mild, efficient and substrate tolerant. Transmetallation of the Pd^{II} complex of macrocycle

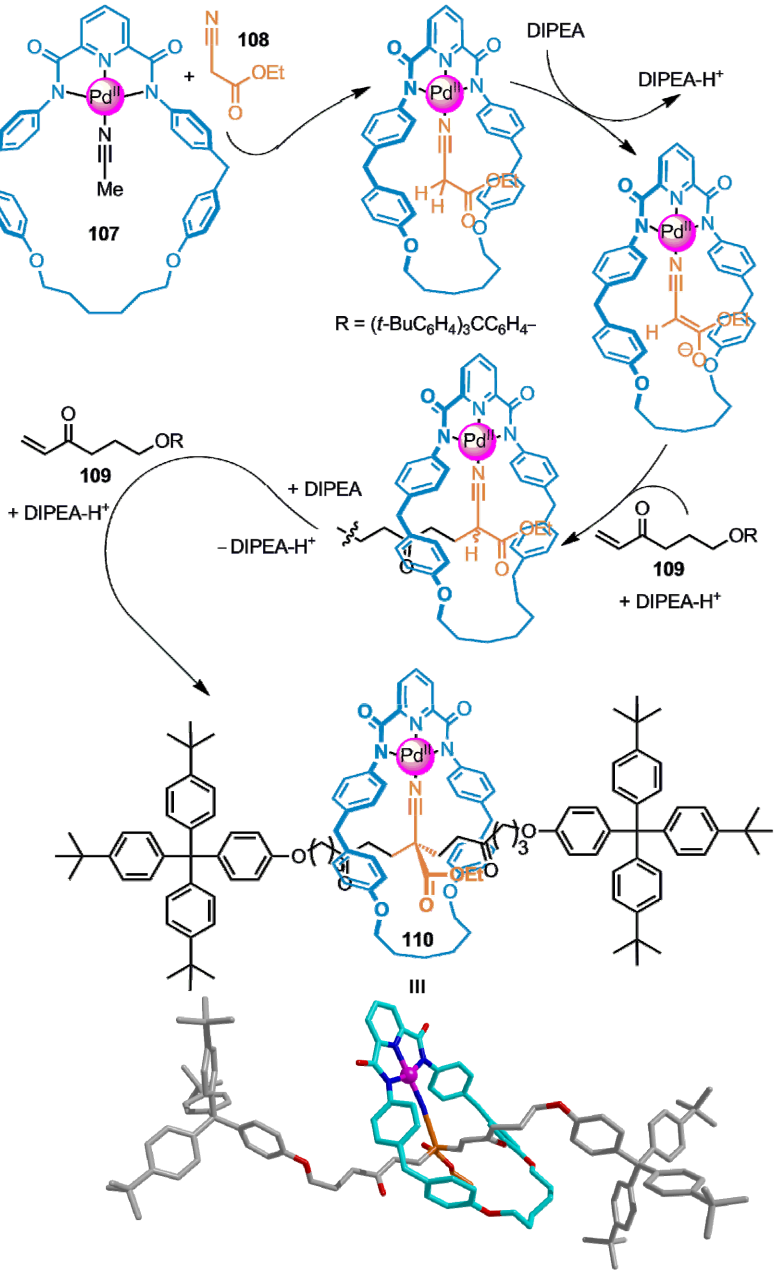
92 with stoppered boronic acid **104** on one face of the macrocycle could be followed by substitution of the remaining acetate ligand by a stoppered electron deficient alkene **105** on the opposite face. Migratory insertion to form a new C–C bond, followed by β-hydride elimination furnished rotaxane **106** in 73% when using only 10 mol% of catalyst (reoxidised *in situ* with benzoquinone and O_2). Notably the catalyst loading could be reduced to as little as 1 mol% without a great deal of reduction in the yield, furthermore a variety of substrates were shown to be tolerated.

1.4.3.6 Lewis Acid Catalysis

The library of AMT reactions has been further extended by Leigh to encompass Lewis acid catalysis in the form of Pd^{II}-mediated Michael additions[97] and Diels–Alder cycloadditions.[98] Unusually for AMT reactions, in both these cases the template interaction 'lives on' in MIM produced. In theory, this aspect of the AMT strategy allows for recognition sites to be 'programmed in' to the interlocked structure or omitted at will through judicious choice of AMT reaction.

The AMT Michael addition takes the form of a multicomponent assembly process in which two successive Michael additions to a Pd^{II}-coordinated cyanoacetate ligand occur sequentially to afford rotaxane. In one example, ethyl cyanoacetate **108** was ligated by Pd–tridentate macrocycle complex **107** and thus activated the methylene protons adjacent to the Pd^{II} center to deprotonation by Hünigs base (Scheme 1.33). Michael addition of the resulting enolate to a stoppered vinyl ketone **109** followed by a second deprotonation and Michael addition cycle on the opposite face of the macrocycle afforded rotaxane **110** in up to 99% under optimized conditions.

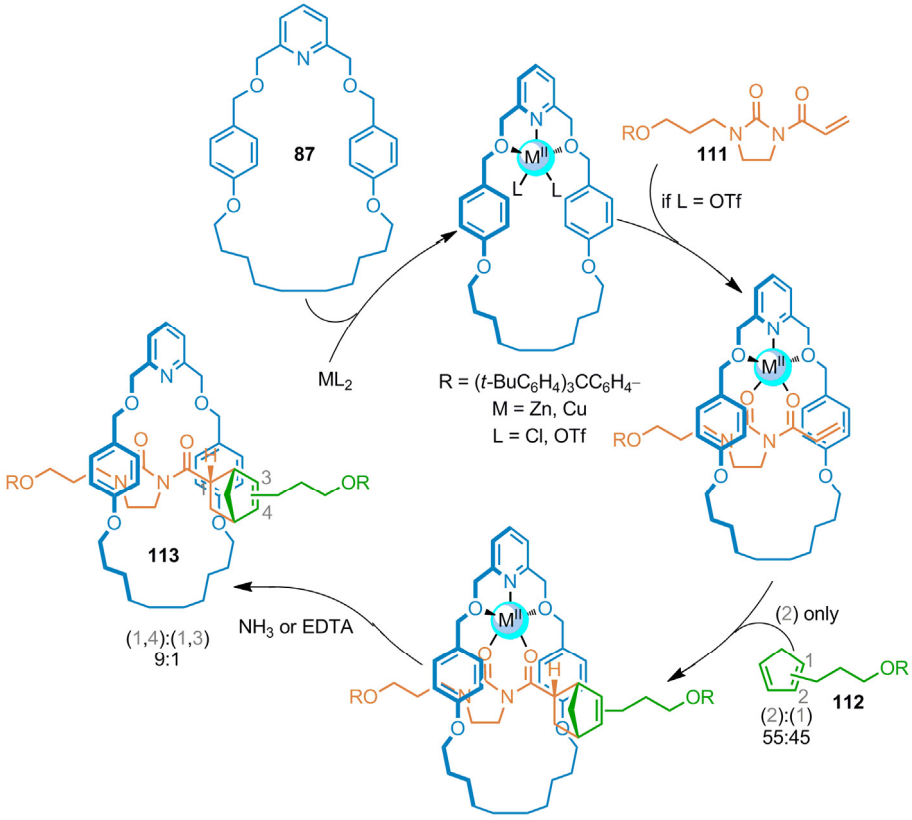
Scheme 1.33. Multicomponent assembly of rotaxane **110** by AMT Michael addition.



An AMT [2]rotaxane synthesis was reported in 2010 in which a macrocycle-bound Zn^{II} or Cu^{II} Lewis acid catalyzed a Diels–Alder cycloaddition between a stoppered diene and a stoppered dienophile. Coordination of the Lewis acid metal salt with macrocycle such as **87**—acting in this case as a tridentate ligand through the pyridine nitrogen and weakly coordinating ether oxygen atoms cf. its monodentate behavior in the CuAAC reaction—resulted in a metal–ligand geometry with replaceable ligands

projecting out of each face of the macrocycle. Stoppered acryloyl imidazolidone **111** could displace the halide or pseudohalide ligands to generate a threaded complex in which the double bond is both exposed and activated towards reaction with a diene (Scheme 1.34). Through use of a stoppered diene the ensuing cycloaddition resulted in rotaxane formation under optimized conditions, as a mixture of endo- and exo-adducts, in up to a 91% yield.

Scheme 1.34. The AMT Diels-Alder Cycloaddition Reaction.

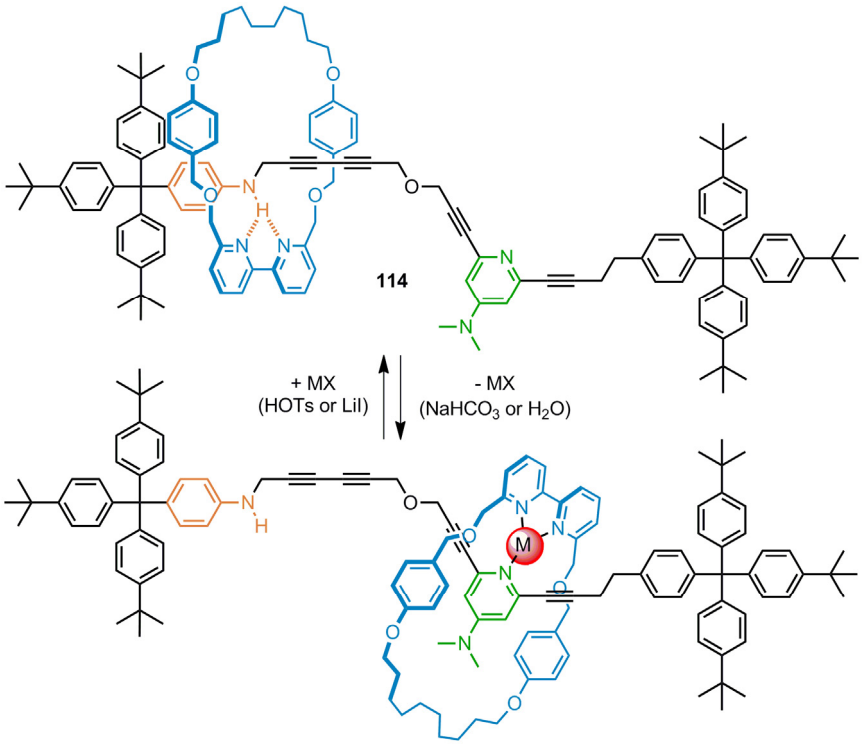


1.4.3.7 Beyond Simple [2]Rotaxanes

The AMT reactions developed by Leigh et al. have, for the most part, only been applied to the synthesis of [2]rotaxanes. Through the design of appropriate 'half-thread' reactants the AMT strategy has been exploited to access molecular shuttles – rotaxanes in which the macrocycle can reside over discrete binding sites or 'stations' and external stimuli can be used to induce 'shuttling' of the macrocycle between stations through Brownian motion. Assembly of degenerate metal-complexed

molecular shuttles was achieved using the CuAAC and Michael addition AMT reactions whereas the Diels-Alder AMT reaction has been harnessed to construct a shuttle with two different stations, controlled by metal complexation. A molecular shuttle with weak intercomponent interactions **114** was accessed via an AMT Cadiot—Chodkiewicz reaction.[91] Assembly of such a shuttle using traditional passive templates would be virtually impossible as the strong template interaction used in the assembly process usually persists in the rotaxane product. A solitary intercomponent hydrogen bond determines the minimum energy co-conformation in each of the two well-defined states (Scheme 1.35). This relatively weak interaction was proposed to permit fast shuttling dynamics upon switching of the relative binding affinities by reversible Li^+ complexation or protonation the macrocycle.

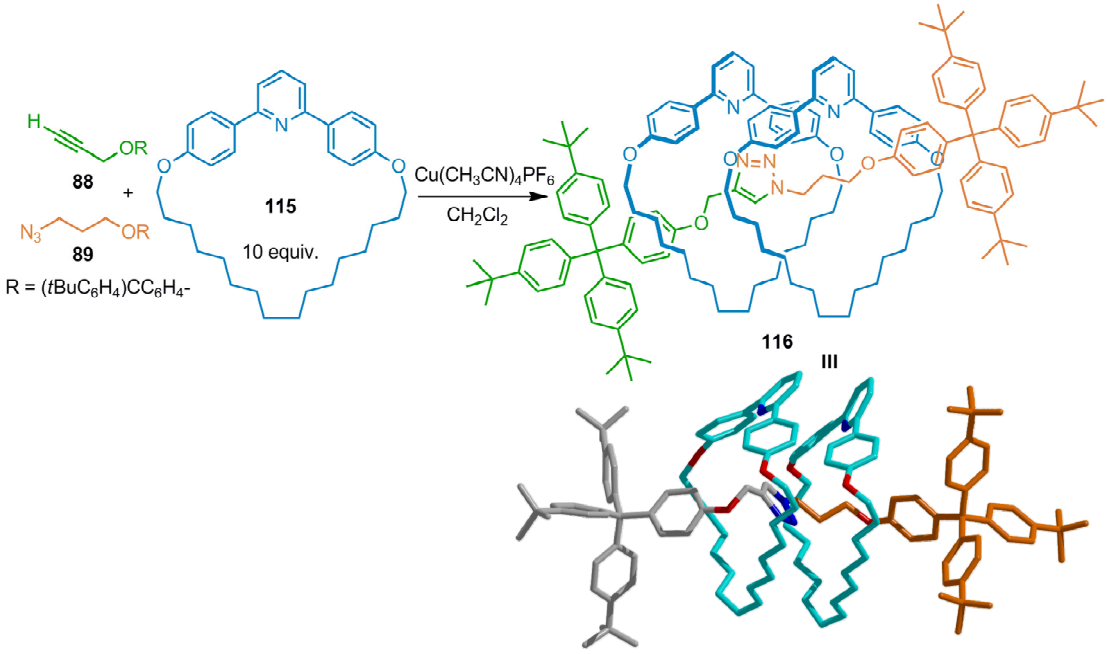
Scheme 1.35. A molecular shuttle with weak intercomponent interactions.



During mechanistic studies into the CuAAC AMT reaction [3]rotaxane **116** with two rings trapped around one axle was synthesized unexpectedly when testing reaction conditions with a particularly high macrocycle to Cu^I ratio (Scheme 1.36). This chance discovery provided a vital clue towards the bimetallic nature of one of the key

reactive intermediates allowing the reaction mechanism to be unraveled. Similarly, a two-ring-one-axle [3]rotaxane was isolated as an unexpected by-product during the synthesis of a molecular shuttle via an AMT Michael addition reaction.

Scheme 1.36. Serendipitous CuAAC [3]rotaxane synthesis.



1.4.3.8 Recent Developments

The synthesis of macrobicyclic [3]rotaxanes via AMT CuAAC and Pd^{II} alkyne homocoupling reactions (*Chapter 3*)[99] and an alkyl thread [2]rotaxane assembled using a sp^3–sp^3 C–C bond forming AMT reaction (*Chapter 2*)[100] have recently been reported and are discussed later in this Thesis. The AMT synthesis of [2]catenanes has also been reported recently, both as part of the work presented in this Thesis (*Chapter 4*)[101] and by Saito and co-workers.[102]

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6. Mathematically, the simplest knot is the trivial– or un–knot, with no crossing points.

7. The originally stated yield of 1% was subsequently downgraded to be several powers of ten less than previously reported – Wasserman, E. *Sci. American* **1962**, *207*, 94.

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CHAPT. 2 | LIGAND-ASSISTED NICKEL-CATALYZED SP^3–SP^3 HOMOCOUPLING OF UNACTIVATED ALKYL BROMIDES AND ITS APPLICATION TO THE ACTIVE TEMPLATE SYNTHESIS OF ROTAXANES

Published as *'Ligand-assisted nickel-catalysed sp^3–sp^3 homocoupling of unactivated alkyl bromides and its application to the active template synthesis of rotaxanes'*– Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, *1*, 383–386.

Synopsis

This Chapter discusses the development of an efficient, mild and operationally simple Ni-catalyzed sp^3-carbon-to-sp^3-carbon homocoupling of unactivated alkyl bromides and its application to the active metal template synthesis of an alkyl chain axle [2]rotaxane. The key to the transformation is the use of tridentate nitrogen-donor-atom (terpy or pybox derived) ligands which inhibit competing β-hydride elimination of alkyl-Ni intermediates.

Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Dr. Roy McBurney developed the synthetic route towards macrocycle **1** which was subsequently optimized and repeated by the Author. Dr. Stephen Goldup conceived of the overall project idea, provided invaluable guidance throughout the project and wrote the published work together with the Author. Prof. Alexandra Slawin solved the crystal structure of **16** and Andrew Plant provided helpful advice and suggestions with regards to the substrate scope of the homocoupling reaction.

2.1 Introduction

Several of the earliest rotaxanes to be rationally synthesized consisted of rings threaded onto simple alkyl chain axles terminated by bulky 'stoppering' groups.[1] The subsequent development[2] of template approaches dramatically increased the efficiency of rotaxane forming reactions,[3] however usually at the cost that permanent recognition elements to direct the interlocking need to be built into both components. Active template methods, [4,5] in which transition metal ions act as both the template for the threaded architecture and as the catalyst for the covalent bond forming reaction that captures the interlocked structure, remove the requirement for a recognition motif in the thread. Nevertheless, the active template synthesis of alkyl chain rotaxanes has not previously been demonstrated, in part because sp^3-sp^3 C-C bond forming reactions are particularly challenging to achieve. Here we describe an active template rotaxane-forming reaction that achieves this difficult construction using a Ni-mediated homocoupling of bromoalkanes. The search for a successful active template system for alkyl chain rotaxane synthesis led to the discovery of this potentially useful catalytic transformation—a novel, mild dehalogenative homocoupling of unactivated alkyl bromides.

2.1.1 Transition Metal Catalyzed sp^3-Carbon to sp^3-Carbon Bond Forming Reactions

The paucity of effective, catalytic, transition-metal-mediated sp^3-sp^3 C-C bond forming reactions is largely due to the slow rates of oxidative addition of metal centres to sp^3-carbon-halogen (and other heteroatom) bonds and the propensity of the resulting organometallic intermediates to undergo β-hydride elimination.[6,7] Successful sp^3-carbon-to-sp^3-carbon coupling protocols are generally limited to halides that are activated towards oxidative addition and lack β-hydrogen atoms (for example, allylic and benzylic chlorides).[8] Recently, the coupling of unactivated alkyl halides with alkyl organometallics under mild conditions using highly reactive Pd and Ni catalysts has been reported.[9-12] The Ni-mediated reactions disclosed[11,12] by Fu and

co-workers are particularly noteworthy as they allow racemic secondary bromides to be cross-coupled with alkyl nucleophiles with excellent enantioselectively.[12]

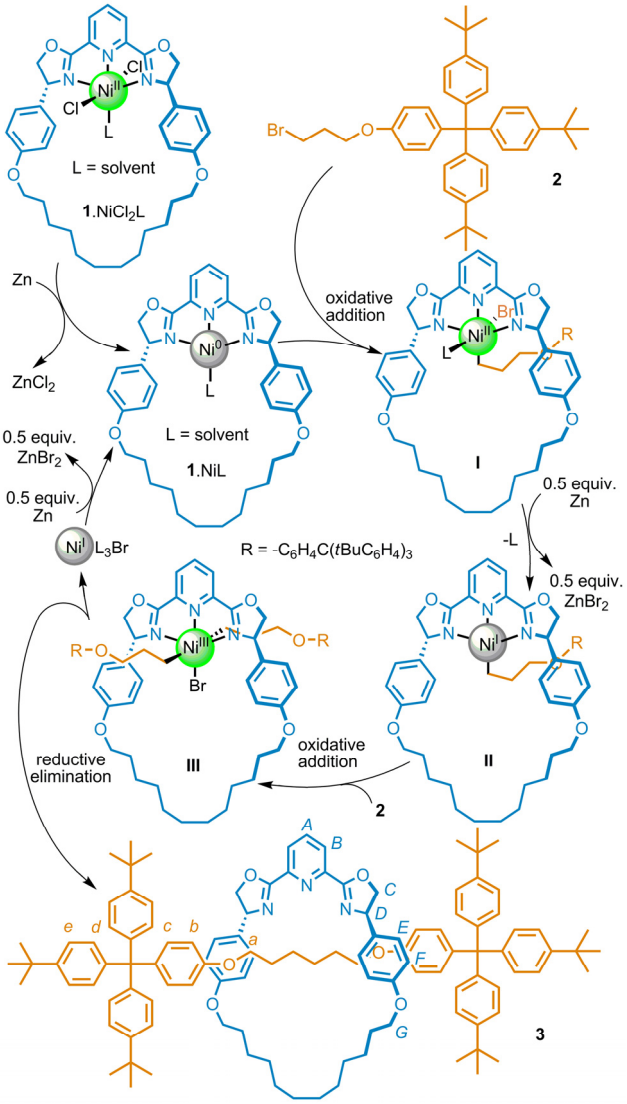
2.2 Results and Discussion

2.2.1 Active Template Synthesis of an Alkyl Chain Axle Rotaxane

We chose the Negishi system developed by Fu and co-workers as a starting point for our investigations into an active template alkyl-chain-forming reaction as it employs a pyridine-2,6-bisoxazoline (pybox) ligand[12] that molecular modeling indicated[13] could create a rigid endotopic coordination site when incorporated into an appropriate macrocyclic scaffold. Macrocycle **1** was synthesized in 10 steps from commercially available materials (*vide infra – Section 2.4*).

We initially focused on the reaction of a bulky alkyl bromide with its corresponding zincate—effectively a homocoupling as the zincate is derived from the bromide—reasoning that the formation of the zincate and the subsequent Ni-mediated coupling reaction might be carried out simultaneously in one pot. Pleasingly, stirring macrocycle **1**, 1 equiv. of $NiCl_2$•DME (dimethoxyethane) and 2.2 equiv. of bromide **2** in the presence of 4 equiv. of activated Zn in THF-*N*-methyl-2-pyrrolidone (NMP) at 80 °C over 18 h led to the formation of [2]rotaxane **3** (Scheme 2.1) as evidenced by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry. Although ^{1}H NMR indicated complete consumption of macrocycle **1**, isolation of [2]rotaxane **3** proved difficult as the pybox moiety of the macrocycle was unstable to chromatography on silica gel and also, to some extent, to the conditions of the reaction itself. Purification using reverse phase silica gel gave a modest isolated rotaxane yield of 24%.

Scheme 2.1. Rotaxane synthesis via a novel Ni-mediated active template sp^3-carbon-sp^3-carbon coupling reaction.



Reagents and conditions: **2** (2.2 equiv.), $NiCl_2$•DME (1 equiv.), Zn (4 equiv.), NMP-THF (1:1), 80 or 25 °C, 18 h, 24% (80 °C) or 46% (25 °C).

Somewhat surprisingly, when the reaction protocol was modified to employ the preformed zincate of **2**,[14] no product was observed. This strongly implied that the homocoupling reaction was not in fact proceeding via a Negishi manifold.[7,12] Replacing activated Zn with Mn powder in the original procedure gave a similar yield of rotaxane **3** indicating that the homocoupling reaction does not involve transmetallation of an alkyl organometallic species to Ni, as the formation of RMnX

from Mn^0 should not occur to a significant extent under these conditions.[15] Lowering the reaction temperature to 25 ºC increased the yield of [2]rotaxane **3** to 46%, further evidence that formation of RZnX is not required for the homocoupling reaction.[16]

The results of these experiments are consistent with the mechanistic pathway shown in Scheme 2.1, in which Ni^{II}-alkyl species **I**—produced by oxidative addition of the alkyl bromide to **1**.Ni^0L—is reduced to the Ni^I-intermediate **II** by Zn, which then oxidatively adds to another equivalent of the alkyl bromide. The isolation of the interlocked product indicates that this oxidative addition must proceed through the cavity of the macrocycle to give threaded complex **III** which then reductively eliminates in a concerted fashion to give [2]rotaxane **3**. The resulting Ni^I complex can then be reduced to Ni^0 by Zn and restart the catalytic cycle.[17] This mechanism is similar to that accepted for the Ni-mediated coupling of aryl halides[18] and that proposed for the dehalogenative cross-coupling of aryl and alkyl halides.[15]

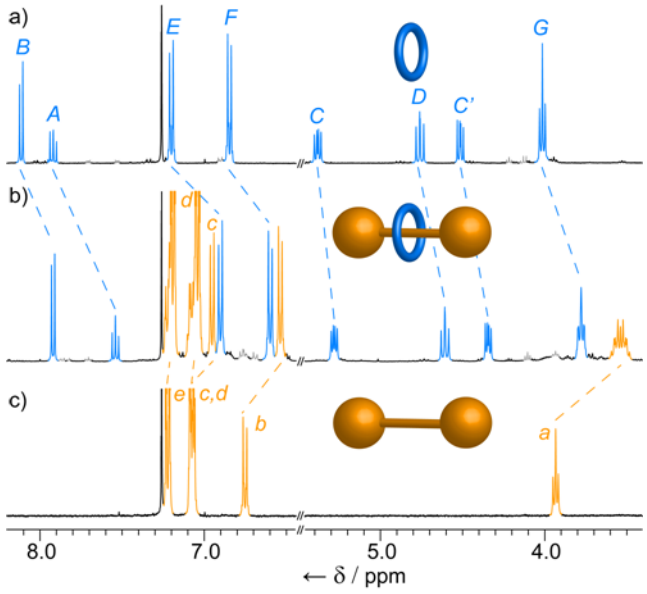


Figure 2.1. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) macrocycle **1**, b) [2]rotaxane **3**, and c) non-interlocked thread. The assignments correspond to the lettering shown in Scheme 2.1.

The interlocked structure of [2]rotaxane **3** was confirmed by comparison of its ^{1}H NMR spectrum with the spectra of the corresponding non-interlocked macrocycle **1** and thread (Figure 2.1). The shielding effects typical of face-on interactions of

aromatic rings in interlocked architectures are observed for several of the resonances present in **3**. Furthermore the signal corresponding to H_a is more complex in the rotaxane than the thread due to the chiral environment of the macrocycle which renders these protons diastereotopic.

2.2.2 General Ni-Catalyzed sp^3-Carbon-sp^3-Carbon Homocoupling of Unactivated Alkyl Bromides

Although metal-promoted sp^2-carbon-sp^2-carbon homocouplings are well known,[19] the metal-catalyzed sp^3-carbon-sp^3-carbon homocoupling of unactivated alkyl halides has not previously been described.[17,20] The classic Wurtz coupling[21] can bring about this type of transformation, but it is seldom used in a practical context as it requires stoichiometric quanitites of highly reactive metals (e.g. Na) and normally gives low yields due to competing elimination and rearrangement processes. The harsh conditions for Wurtz couplings are only compatible with a few functional group types, a problem shared by sp^3-carbon-sp^3-carbon bond forming reactions between Grignard reagents and alkyl halides or sulfonates. One of the most popular ways to couple molecular fragments via a sp^3-carbon-sp^3-carbon bond is through ring closing (intramolecular) or cross (intermolecular) olefin metathesis followed by hydrogenation of the resulting internal alkene.[22] Accordingly, a mild general method for the dehalogenative homocoupling of unactivated alkyl bromides to form C-C bonds potentially has wide practical utility and so we performed an optimization study (Scheme 2.2, Table 2.1) on the catalytic protocol discovered above and explored the generality of the transformation (Table 2.2).

When 1-bromo-3-phenoxypropane **5** was treated with Ni^{II} and acyclic pybox ligand **4** (replacing macrocycle **1**), under the conditions developed for the active template reaction, **6** was isolated in essentially quantitative yield (>95%, Table 2.1, entry 1). This indicates that the homocoupling reaction itself is extremely efficient and supports the notion that the yield of rotaxane **3** is limited by the stability of the macrocycle under the reaction conditions. It proved possible to reduce the loading of Ni^{II} to 5 mol% (entry 3) without any significant reduction in product yield, but lower

catalyst loadings were less effective (entry 4). Replacing chiral ligand **4** with achiral tridentate ligand 2,2':6',2"-terpyridine (**7**) led to a slight reduction in yield (entry 5) which was improved when cheap, air stable, $NiCl_2•(H_2O)_6$ was substituted for air sensitive $NiCl_2$•DME (entry 6). Changing solvent to DMF improved both the reaction yield with the $NiCl_2•(H_2O)_6$ catalyst (entry 7) and the reaction rate (entry 8). The crucial role played by the tridentate ligand[10] (**4** or **7**) was demonstrated by control reactions with bidentate (**8**) and monodentate (**9**) analogues (entries 9 and 10) or the absence of any ligand (entry 11), each of which resulted in virtually no product being formed.

Scheme 2.2. Ligand-assisted Ni-catalyzed homocoupling of 1-bromo-3-phenoxypropane. For reagents and conditions see Table 2.1.

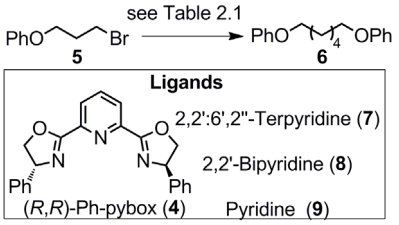
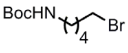
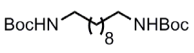
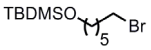
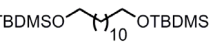
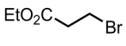
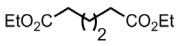
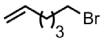
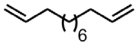
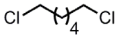
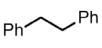
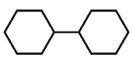
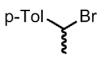
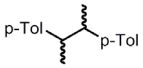


Table 2.1. Optimization of the conditions, ligand and nickel source for the Ni-catalyzed homocoupling of 1-bromo-3-phenoxypropane (Scheme 2.2).

Entry	Ni Source (mol%)	Ligand	Yield/%	Time /h
1[a]	$NiCl_2$•DME (50)	**4**	>95[c]	18
2[a]	$NiCl_2$•DME (12.5)	**4**	>95[c]	18
3[a]	$NiCl_2$•DME (5)	**4**	93[d]	18
4[a]	$NiCl_2$•DME (2.5)	**4**	50[c]	18
5[a]	$NiCl_2$•DME (5)	**7**	86[d]	18
6[a]	$NiCl_2•(H_2O)_6$ (5)	**7**	88[d]	18
7[b]	$NiCl_2•(H_2O)_6$ (5)	**7**	95[d]	18
8[b]	$NiCl_2•(H_2O)_6$ (5)	**7**	95[d]	1
9[b]	$NiCl_2•(H_2O)_6$ (5)	**8**	<5[c]	18
10[b]	$NiCl_2•(H_2O)_6$ (5)	**9**	<5[c]	18
11[b]	$NiCl_2•(H_2O)_6$ (5)	-	0	18

[a] Reagents and conditions: **5** (1 equiv.), Zn (1 equiv.), NMP-THF (1:1), rt; [b] DMF; [c] Yield assessed by GCMS analysis; [d] Isolated yield.

Table 2.2. Substrate scope for the 2,2':6',2"-terpyridine (**7**)-assisted Ni-catalyzed homocoupling of alkyl bromides.[a]

Entry	Substrate	Product	Yield/%
1			97
2			96
3[b]			78
4			>99
5			>99
6			95
7			>99
8			80[c]

[a] $NiCl_2•(H_2O)_6$, 2,2':6',2"-terpyridine **7**, DMF, 4 h, rt; [b] 18 h; [c] 1:1 mixture of diastereoisomers. p-Tol = 4-$CH_3C_6H_4$-.

The substrate scope of the reaction was also investigated (Table 2.2). The reaction tolerates standard oxygen and nitrogen function protecting groups well (entries 1 and 2), including modestly acidic NH groups (entry 1) and esters (entry 3; longer reaction times were required here, possibly due to chelation of the Ni by the ester carbonyl). Alkenyl substrates are also compatible with the reaction (entry 4). The absence of cyclopentane byproducts when using this substrate suggests that radical pathways are not in operation[10] during the oxidative addition and reductive elimination steps, a finding reinforced by the formation of the threaded product during the active template reaction (Scheme 2.1). Clear selectivity between C-Br and C-Cl bonds is demonstrated by the chemoselective reaction of 1,3-chlorobromopropane (entry 5). Homocoupling of benzyl bromide proceeds in high yield (entry 6) and coupling of bromocyclohexane is essentially quantitative (entry 7) showing that secondary alkyl bromides are also highly effective substrates for this reaction. Although the dimerization of a racemic secondary bromide proceeded in good yield (entry 8), no selectivity between the chiral and meso diasteroisomers was observed (*d.r.* = 1:1). Repeating this reaction using (*R*,*R*)-Ph-pybox **4** gave no change in the

diastereoisomeric ratio suggesting that the stereoconvergent process demonstrated[12] by Fu and co-workers in their Negishi cross-couplings of racemic alkyl halides does not appear to operate in this system.

2.3 Conclusions

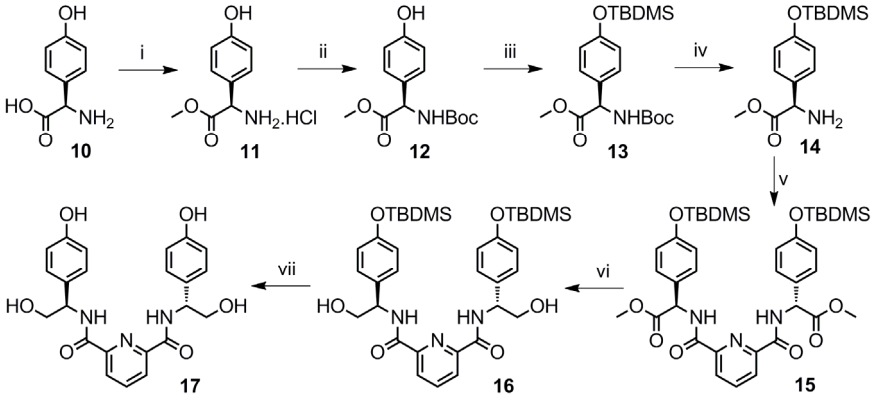
Through the search for an sp^3-carbon-sp^3carbon bond forming active template reaction to produce an alkyl chain axle rotaxane, we have developed a high yielding general method for the homocoupling of primary and secondary alkyl bromides. This ligand-assisted nickel-catalyzed procedure is operationally simple, efficient and cheap and may prove to be broadly applicable. Active template rotaxane synthesis not only represents an advanced strategy for the construction of mechanically interlocked molecules but, as exemplified here, can also serve as an effective conduit for reaction discovery.[5]

2.4 Experimental Details

Stoppered alkyl bromide **2**[4c], *N*,*N*'-*di*-boc-decamethylendiamine[23] and 1-(1-bromoethyl)-4-methylbenzene[12b] were prepared according to literature procedures.

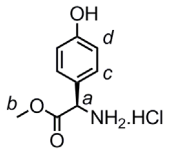
2.4.1 Synthesis of Macrocycle 1

Scheme 2.3. Synthesis of **17** from (*R*)-4-hydroxyphenylglycine **10**.



Reagents and conditions: (i) $SOCl_2$, MeOH, 0 °C to rt, 18 h, 99%; (ii) Boc_2O, Et_3N, THF, reflux, 18 h, 99%; (iii) TBDMSCl, imidazole, DMF, 0 °C to rt, 18 h, 99%; (iv) TFA, CH_2Cl_2, 18 h, 83%; (v) 2,6-pyridinedicarbonyl dichloride, Et_3N, THF, 0 °C to rt, 18 h; (vi) $NaBH_4$, THF, MeOH, 70%; (vii) AcCl, MeOH, 48 h, 92%.

(*R*)-4-Hydroxyphenylglycine methyl ester hydrochloride

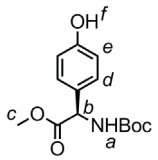


11

To a suspension of (*R*)-4-hydroxyphenylglycine (19.3 g, 115 mmol) in MeOH (120 mL) at 0 °C was added dropwise $SOCl_2$ (10.9 mL, 150 mmol). The solution was allowed to warm to room temperature and stirred for 18 h. The solvent was removed under reduced pressure to yield the title compound **11**[24] as a colorless solid (25.1 g, >99%). The product was used without further purification. M.p. 180 ºC (dec.); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.28 (d, 2H, J = 8.6, H_c) 6.85 (d, 2H, J = 8.6, H_d),

5.08 (s, 1H, H_a), 3.80 (s, 3H, H_b); ^{13}C NMR (100 MHz, CD_3OD): δ = 169.0, 158.9, 129.2, 122.2, 115.7, 55.7, 52.4; LRFAB-MS (3-NOBA matrix): *m/z* = 182 $[M\text{-}Cl]^+$.

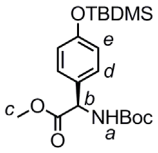
(*R*)-*N*-(*t*Butoxycarbonyl)-4-hydroxyphenylglycine methyl ester



12

A solution of **11** (33.0 g, 0.152 mol), Boc_2O (33.1 g, 0.152 mol) and Et_3N (25.6 mL, 0.182 mol) in THF (150 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure and the crude residue was redissolved in $CHCl_3$ (300 ml). The organic layer was washed with 1 M HCl (2 x 150 mL), water (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the title compound **12**[25] as a colorless solid (43.0 g, >99%). The product was used without further purification. M.p. 139 ºC; $[\alpha]_D^{20}$ = -159.6 (*c* = 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, 2H, *J* = 8.5, H_d), 6.72 (d, 2H, *J* = 8.5, H_e), 6.07 (s, 1H, H_f), 5.59 (d, 1H, *J* = 7.1, H_a), 5.22 (1H, d, *J* = 7.1, H_c), 3.70 (s, 3H, H_c), 1.35 (s, 9H, H_{Boc}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 156.2, 155.1, 151.0, 128.3, 115.8, 80.5, 57.0, 52.8, 28.3; LRFAB-MS (3-NOBA matrix): *m/z* = 282 $[MH]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 282.1347 (calcd. for $C_{14}H_{20}NO_5$, 282.1341).

(*R*)-*N*-(*t* Butoxycarbonyl)-4-(*t*-butyldimethylsiloxyphenyl)glycine methyl ester

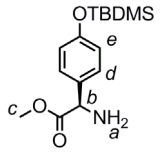


13

To a solution of **12** (8.64 g, 30.7 mmol) in DMF (20 mL) at 0 ºC was added imidazole (4.180 g, 61.4 mmol) and TBDMSCl (5.09 g, 33.8 mmol). The solution was allowed

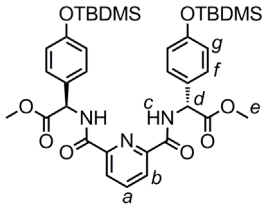
to warm to rt and stirred for 18 h. The solvent was removed under reduced pressure and the resultant oil was redissolved in CH_2Cl_2 (150 mL), washed with 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the title compound **13**[24] as a yellow oil (12.4 g, >99%). The product was used without further purification. $[\alpha]_D^{21}$ = -4.8 (c = 2.5, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, 2H, J = 8.5, H_d), 6.80 (d, 2H, J = 8.5, H_e), 5.45 (d, 1H, J = 7.1, H_a), 5.24 (d, 1H, J = 7.1, H_b), 3.72 (s, 3H, H_c), 1.44 (s, 9H, H_{Boc}), 0.98 (s, 9H, H_{silyl}), 0.19 (s, 6H, H_{silyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 155.9, 145.4, 138.6, 137.2, 130.1, 128.3, 120.4, 57.0, 52.6, 36.5, 28.3, 25.6; LRFAB-MS (3-NOBA matrix): m/z = 396 $[MH]^+$; HRFAB-MS (THIOG matrix): m/z = 396.2206 (calcd. for $C_{20}H_{34}NO_5Si$, 396.2206).

(*R*)-4-(*t*-Butyldimethylsiloxy)phenylglycine methyl ester



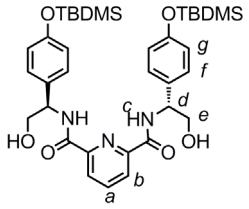
14

To a solution of **13** in CH_2Cl_2 (180 mL) was added TFA (20 mL), the solution was stirred for 18 h. The reaction was diluted with CH_2Cl_2 (70 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 200 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the title compound as a yellow oil (4.49 g, 83%). The compound was used without further purification. $[\alpha]_D^{21}$ = -3.1 (c = 2.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, 2H, J = 8.6, H_d), 6.81 (d, 2H, J = 8.6, H_e), 4.56 (s, 1H, H_b), 3.70 (s, 3H, H_c), 2.00 (br, 2H, H_a), 0.98 (s, 9H, H_{silyl}), 0.19 (s, 6H, H_{silyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 166.9, 155.5, 132.8, 128.0, 120.2, 55.7, 52.4, 25.6, 18.1; LRFAB-MS (3-NOBA matrix): m/z = 294 $[M\text{-}H]^+$; HRFAB-MS (THIOG matrix): m/z = 294.1525 (calcd. for $C_{15}H_{24}NO_3{}^{28}Si$, 294.1525).



15

To a solution of **14** (4.49 g, 15.2 mmol) and Et_3N (2.9 mL, 20.7 mmol) in THF (150 mL) at -78 ºC was added dropwise a solution of 2,6-pyridinedicarbonyl dichloride (1.407 g, 6.9 mmol) in THF (20 mL) over a period of 1 h. The solution was allowed to warm to rt and stirred for 18 h. The resulting suspension was filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (30:70 EtOAc-petrol) to yield the title compound as a yellow oil (4.73 g, 95%). $[\alpha]_D^{20}$ = +6.9 (c = 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, 2H, J = 7.2, H_c), 8.32 (d, 2H, J = 7.8, H_b), 8.01 (t, 1H, J = 7.8, H_a), 7.38 (d, 4H, J = 8.6, H_f), 6.87 (d, 4H, J = 8.6, H_g), 5.69 (d, 2H, J = 7.2, H_d), 3.79 (s, 6H, H_e), 0.98 (s, 18H, H_{silyl}), 0.20 (s, 12H, H_{silyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 157.5, 156.0, 148.3, 139.1, 128.8, 128.4, 125.3, 120.5, 56.1, 52.9, 25.6, 23.4, 18.1; LRFAB-MS (3-NOBA matrix): m/z = 722 $[MH]^+$; HRFAB-MS (THIOG matrix): m/z = 722.3290 (calcd. for $C_{37}H_{52}N_3O_8Si_2$, 722.3292).

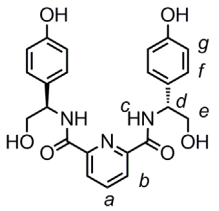


R,R-**16**

To a solution of **15** (3.41, 4.7 mmol) in THF (42 mL) and MeOH (7 mL) was added $NaBH_4$ (0.428 g, 11.3 mmol). After 75 min, TFA (1 mL) was added and the solvent was removed under reduced pressure. The crude residue was redissolved in EtOAc (300 mL), washed with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated under

reduced pressure and purified by column chromatography (60:40 EtOAc-petrol). Two diastereoisomers were isolated. The major diastereoisomer, *R*,*R*-**16**, was obtained as a colorless solid (2.19 g, 70%) and used for subsequent reactions. Analytical data for *R*,*R*-**16**: R_f = 0.22 (EtOAc): $[\alpha]_D^{20}$ = +50.4 (c = 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, 2H, J = 7.2, H_c), 8.35 (d, 2H, J = 7.7, H_b), 8.06 (t, 1H, J = 7.7, H_a), 7.26 (d, 4H, J = 8.5, H_f), 6.86 (d, 4H, J = 8.5, H_g), 5.21 (q, 2H, J = 7.2 Hz, H_d), 3.98 (br, 4H, H_e), 0.98 (s, 18H, H_{silyl}), 0.20 (s, 12H, H_{silyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 155.3, 148.5, 139.0, 131.5, 127.8, 125.1, 120.3, 66.0, 54.9, 25.6, 18.1, 1.0; LRFAB-MS (3-NOBA matrix): m/z = 664 $[M\text{-}H]^+$; HRFAB-MS (THIOG matrix): m/z = 664.3238 (calcd. for $C_{35}H_{50}N_3O_6{}^{28}Si_2$, 664.3238).

Minor diastereoisomer, *meso*-**16**: R_f = 0.08 (EtOAc); M.p. 174 ºC; $[\alpha]_D^{20}$ = 0.0 (c = 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, 2H, J = 8.3, H_c), 8.16 (d, 2H, J = 7.8, H_b), 7.86 (t, 1H, J = 7.8, H_a), 6.78 (d, 4H, J = 8.5, H_g), 5.25 (dt, 2H, J = 5.2, 8.3, H_d), 3.89 (d, 4H, J = 5.2, H_e), 0.96 (s, 18H, H_{silyl}), 0.16 (s, 12H, H_{silyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 155.4, 148.5, 139.2, 131.3, 127.8, 125.1, 120.4, 66.5, 55.1, 31.0, 25.6, 18.1; LRFAB-MS (3-NOBA matrix): m/z = 688 $[MNa]^+$; HRFAB-MS (3-NOBA matrix): m/z = 688.3235 (calcd. for $C_{35}H_{51}N_3O_6NaSi_2$, 688.3208).

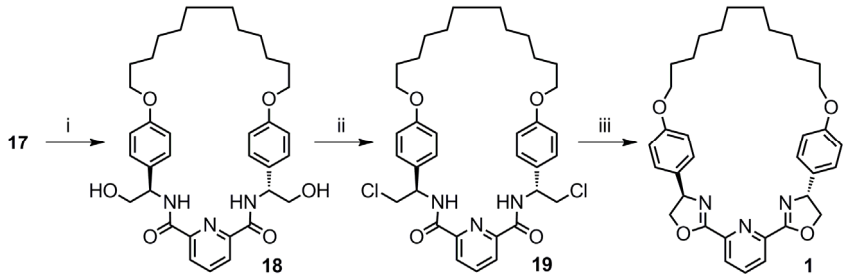


17

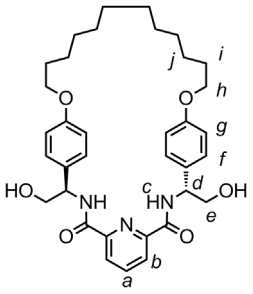
R,*R*-**16** (4.675 g, 7.02 mmol) was dissolved in MeOH (70 mL) and AcCl (0.12 mL, 2.1 mmol) was added. The solution was stirred for 48 h. The resultant suspension was filtered to yield the title compound as a white solid (2.822 g, 92%) The product was used without further purification. M.p. 241 ºC; $[\alpha]_D^{21}$ = +73.1 (c = 0.52, MeOH); ^{1}H

NMR (400 MHz, CD_3OD): δ = 8.28 (d, 2H, J = 7.4, H_b), 8.14 (t, 1H, J = 7.4, H_a), 7.28 (d, 4H, J = 8.6, H_f), 6.78 (d, 4H, J = 8.6, H_g), 5.20 (t, 2H, J = 5.9, H_d), 3.93 (t, 4H, J = 5.9, H_e); ^{13}C NMR (100 MHz, CD_3OD): δ = 165.5, 159.1, 150.0, 140.6, 130.1, 127.8, 126.4, 116.7, 58.0, 53.2; LR-FABMS (3-NOBA matrix): *m/z* = 438 $[MH]^+$; HR-FABMS (3-NOBA matrix): *m/z* = 438.1652 (calcd. for $C_{23}H_{24}N_3O_6$, 438.1659).

Scheme 2.4. Synthesis of pybox macrocycle **1**.



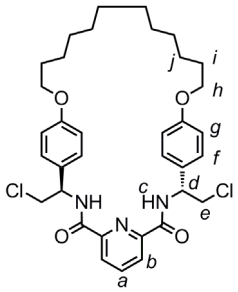
Reagents and conditions: (i) 1,12-dibromododecane, K_2CO_3, DMF, 100 ºC, 22%; (ii) $SOCl_2$, $CHCl_3$, reflux, 8 h, 70%, (iii) TBAF, THF, 4 h, 79%.



18

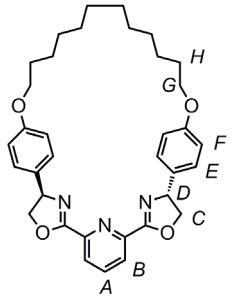
To a solution of **17** (1.50 g, 3.4 mmol) and 1,12-dibromododecane (1.116 g, 3.4 mmol) in DMF (1 L) was added K_2CO_3 (19.0 g, 13.7 mmol). The suspension was stirred at 100 ºC for 48 h. The solvent was removed under reduced pressure, and the crude residue was redissolved in water (100 mL) and extracted into CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography (1:99 MeOH-EtOAc) to yield the title compound as a colorless solid (0.450 g, 22%). M.p. 91 ºC; $[\alpha]_D^{22}$ =

+13.9 (c = 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, 2H, J = 7.8, H_b), 8.10 (d, 2H, J = 5.6 Hz, H_c), 8.07 (t, 1H, J = 7.8, H_a), 7.27 (d, 4H, J = 8.6, H_g), 6.95 (d, 4H, J = 8.6, H_f), 5.17 (m, 2H, H_d), 3.99 (m, 4H, H_h), 3.96 (m, 4H, H_e), 1.81 (m, 4H, H_i), 1.50 (m, 4H, H_j), 1.32 (br, 12H, H_{alkyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 159.1, 148.2, 139.2, 130.3, 127.9, 125.2, 115.1, 68.0, 66.6, 56.6, 28.9, 28.8, 28.4, 27.9, 25.4; LR-FABMS (3-NOBA matrix): m/z = 604 $[MH]^+$; HR-FABMS (3-NOBA matrix): m/z = 604.3398 (calcd. for $C_{35}H_{46}N_3O_6$, 604.3381).



19

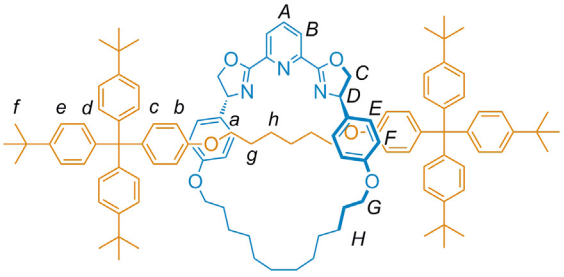
To a solution of **18** (0.450 g, 0.75 mmol) in $CHCl_3$ was added $SOCl_2$ (0.54 mL, 7.5 mmol). The solution was heated at a reflux for 8 h. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (1:19 EtOAc-CH_2Cl_2) to yield the title compound as a colorless solid (0.336 g, 70%). M.p. 92 ºC; $[\alpha]_D^{20}$ = +4.35 (c = 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, 2H, J = 7.8, H_b), 8.10 (t, 1H, J = 7.8, H_a), 8.09 (d, 2H, J = 7.8, H_c), 7.34 (d, 4H, J = 8.7, H_f), 6.96 (d, 4H, J = 8.7, H_g), 5.41 (q, 2H, H_d), 4.01 (m, 4H, H_h), 3.95 (m, 4H, H_e), 1.81 (m, 4H, H_i), 1.50 (m, 4H, H_j), 1.31 (br, 12H, H_{alkyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 159.3, 148.4, 139.4, 129.7, 127.9, 125.4, 115.0, 67.9, 53.8, 47.4, 28.7, 28.5, 28.0, 27.9, 25.4; LR-FABMS (3-NOBA matrix): m/z = 640 $[MH]^+$; HR-FABMS (3-NOBA matrix): m/z = 640.2719 (calcd. for $C_{35}H_{44}N_3O_4Cl_2$, 640.2703).



1

To a solution of **19** (1.765 g, 2.76 mmol) in THF (30 mL) was added TBAF (1M in THF, 11.0 mL, 11.0 mmol) the solution was stirred for 4 h, after which time the solvent was removed under reduced pressure. The resulting residue was redissolved in CH_2Cl_2 (50 mL) and Et_2O (50 mL) and washed with trisodium citrate (3 x 50 mL), the organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by rapidly filtering through a short pad of silica gel with CH_2Cl_2 to yield the title compound **1** as a colorless solid (1.239 g, 79%). **1** was found to be unstable under acidic conditions and decomposed upon prolonged exposure to silica gel. m.p. 81 ºC; $[\alpha]_D^{22}$ = +38.7 (*c* = 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8, 2H, H_B), 7.91 (t, *J* = 7.8, 1H, H_A), 7.20 (d, *J* = 8.7, 4H, H_E), 6.84 (d, *J* = 8.7, 4H, H_F), 5.38 (dd, *J* = 6.1, 9.8, 2H, H_C), 4.75 (dd, *J* = 8.6, 9.8, 2H, H_D), 4.51 (dd, *J* = 6.1, 8.6, 2H, $H_{C'}$), 4.01 (t, *J* = 6.9 Hz, 4H, H_G), 1.69 (m, 4H, H_H), 1.36 (m, 4H, H_I), 1.22 (br, 12H, $H_{J,K,L}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 156.3, 145.1, 135.5, 132.1, 126.0, 123.5, 113.3, 73.3, 67.5, 65.9, 28.0, 27.8, 27.2, 26.5, 23.8; LR-FABMS (3-NOBA matrix): *m/z* = 568 $[MH]^+$; HR-FABMS (3-NOBA matrix): *m/z* = 568.3169 (calcd. for $C_{35}H_{42}N_3O_4$, 568.3169).

2.4.2 Synthesis of Rotaxane 3



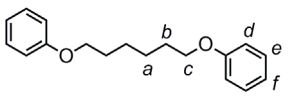
3

To a solution of pybox macrocycle **1** (28 mg, 49 μmol) and $NiCl_2$•diglyme (10 mg, 45 μmol) in THF (1 mL) under an inert atmosphere of nitrogen was added activated zinc (12 mg, 180 μmol) and NMP (1 mL) and the resulting suspension sonicated for 5 min giving color change green/yellow to deep purple. To this was added stoppered bromide **2** (69 mg, 110 μmol) and the resulting mixture stirred at rt for 2.5 h. The reaction mixture was diluted with EtOAc (40 mL) and extracted with 17.5% $NH_{3(aq)}$ saturated with EDTA (2 × 40 mL portions), H_2O (3 × 40 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was diluted with hexane (40 mL) and extracted with acetonitrile (3 × 20 mL). The hexane layer was isolated and concentrated, purification of the resulting residue on a short plug of C_{18} end capped reversed-phase silica (gradient elution: MeOH-THF 1. 9:1 2. 4:1) gave rotaxane **3** (42 mg, 46%). m.p 140 – 143 °C; $[\alpha]_D^{22}$ = -113.3 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1): δ = 7.92 (d, 2H, J = 7.8, H_B), 7.54 (t, 1H, J = 7.8, H_A), 7.19 (d, 12H, J = 8.5, H_g), 7.04 (d, 12H, J = 8.5, H_f), 6.92 (m, 8H, H_e + H_E), 6.56 (m, 8H, H_d + H_F), 5.28 (dd, 1H, J = 5.3, J = 9.4, H_C), 4.60 (t, 1H, J_t = 9.1, H_D), 4.34 (dd, 1H, J = 5.3, J = 8.5, $H_{C'}$), 3.77 (t, 4H, J = 6.5, H_G), 3.53 (m, 4H, H_c), 1.62 (m, 4H, H_H), 1.37 (m, 4H, H_b), 1.23 (br, 74H, H_a + H_h + H_{alkyl}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 158.1, 156.8, 148.0, 146.6, 144.2, 139.0, 133.9, 132.4, 131.8, 130.6, 127.6, 123.9, 114.7, 112.9, 74.9, 69.2, 67.7, 67.3, 62.9, 34.2, 31.3, 25.7, 25.6, 22.6, 14.1; LRFAB-MS (3-NOBA matrix): m/z = 1660 $[MH]^+$; HRFAB-MS (3-NOBA matrix): m/z = 1660.077 $[MH]^+$ (calcd. for $C_{114}H_{140}{}^{13}CO_6N_3$, 1660.077).

2.4.3 General Procedure for the sp^3–sp^3 Homocoupling Reactions of Unactivated Bromides

To a solution of 2,6-bis[(*4S*)-4-phenyl-2-oxazolinyl]pyridine (Ph-pybox) or 2,2':6',2''-terpyridine (terpy) (50 μmol) and $NiCl_2$•$6H_2O$, $NiCl_2$•DME or $Ni(cod)_2$ (bis(cyclooctadiene)nickel(0)) (50 μmol) in DMF (2 mL) under an inert atmosphere of nitrogen was added activated Zn (70 mg, 1 mmol) followed by the unactivated bromide (1 mmol). Upon stirring the suspension turned from light green/blue (pybox/terpy) to deep purple and was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc (40 mL) and extracted with 17.5% $NH_{3(aq)}$ saturated with EDTA (2 × 40 mL portions), 1M HCl (2 x 40 mL), H_2O (3 × 40 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and the solvent and volatile impurities removed under reduced pressure to give the homocoupled product which required no further purification.

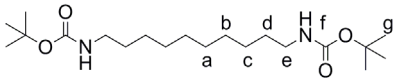
1,6-Dipenoxyhexane



6

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and (3-bromo-propoxy)-benzene (0.17 mL, 1 mmol) in DMF (2 mL) afforded 1,6-dipenoxyhexane **6** (137 mg, 95%) as a colorless solid. Melting point was consistent with published data.[26] M.p. 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.27 (m, 4H, H_e), 6.97-6.90 (m, 6H, H_d and H_f), 3.98 (t, 4H, J = 6.5, H_c), 1.88-1.80 (m, 4H, H_b), 1.59-1.53 (m, 4H, H_a); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 129.3, 120.4, 114.4, 67.6, 29.2, 25.8; LRAPCI-MS: *m/z* = 271.2 $[MH]^+$; HRAPCI-MS: *m/z* = 270.1610 $[M]^+$ (calcd. for $C_{18}H_{22}O_2$, 270.1614).

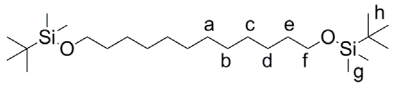
***N,N'-di*-boc-decamethylendiamine**



20

Following the general procedure with terpy (11.8 mg, 50 µmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 µmol), activated Zn (70 mg, 1 mmol) and (5-Bromo-pentyl)-carbamic acid tert-butyl ester (287 mg, 1 mmol) in DMF (2 mL) afforded *N,N'-di*-boc-decamethylendiamine **20 (**195 mg, 97%) as a colorless solid. M.p. 107 °C;[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.54 (br, 2H), 3.02-3.13 (m, 4H, H_e), 1.38-1.48 (m, 22H, H_d and H_g), 1.12-1.29 (m, 12H, H_a, H_b and H_c); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 78.9, 40.5, 29.9, 29.6, 29.3, 29.1, 28.3,. LRAPCI-MS: *m/z* = 373.3 $[MH]^+$; HRESI-MS: *m/z* = 373.3058 $[MH]^+$ (calcd. for $C_{20}H_{41}O_4N_2$, 373.3068).

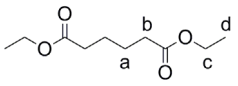
1,12-Bis-(*tert*-butyl-dimethyl-silanyloxy)-dodecane



21

Following the general procedure with terpy (11.8 mg, 50 µmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 µmol), activated Zn (70 mg, 1 mmol) and (6-bromohexyloxy)-*tert*-butyldimethylsilane (303 µL, 1 mmol) in DMF (2 mL) afforded 1,12-bis-(*tert*-butyl-dimethyl-silanyloxy)-dodecane **21 (**223 mg, 96%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, 4H, *J* = 6.7, H_f), 1.46-1.56 (m, 4H, H_e), 1.23-1.33 (m, 16H, H_a, H_b, H_c and H_d), 0.89 (s, 18H, H_h), 0.04 (s, 12H, H_g); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.3, 32.8, 29.6, 29.5, 29.4, 25.9, 25.7, 18.3, -5.2; LRAPCI-MS: *m/z* = 431.4 $[MH]^+$; HRESI-MS: *m/z* = 431.3736 $[MH]^+$ (calcd. for $C_{24}H_{55}O_2Si_2$, 431.3735).

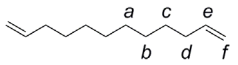
Hexanedioic acid diethyl ester



22

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and ethyl 3-bromopropionoate (138 μL, 1 mmol) in DMF (2 mL) afforded hexanedioic acid diethyl ester **22 (**85 mg, 78%) as a colorless solid. ^{1}H NMR was consistent with published data.[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (q, 4H, J = 7.1, H_c), 2.31-2.24 (m, 4H, H_b), 1.65-1.58 (m, 4H, H_a), 1.21 (t, 6H, J = 7.1, H_d); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 60.3, 33.9, 24.4, 14.2.

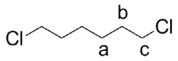
Dodeca-1,11-diene



23

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and bromohexene (144 μL, 1 mmol) in DMF (2 mL) afforded dodeca-1,11-diene **23 (**89 mg, >99%) as a colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with published data.[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (tdd, 2H, J = 6.7, 10.2, 16.9, H_e), 4.95-5.02 (m, 2H, $H_{f'}$), 4.90-4.95 (m, 2H, H_f), 2.00-2.07 (m, 4H, H_d), 1.33-1.41 (m, 4H, H_c), 1.31-1.25 (m, 8H, H_a and H_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 114.0, 33.8, 29.4, 29.1, 28.9.

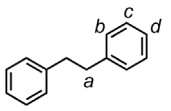
1,6-Dichlorohexane



24

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and 1-bromo-3-chloropropane (106 μL, 1 mmol) in DMF (2 mL) afforded 1,6-dichlorohexane **24 (**96 mg, >99%) as a yellow oil. ^{1}H NMR and ^{13}C NMR were consistent with published data.[30] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (t, 4H, J = 6.6, H_c), 1.75-1.83 (m, 4H, H_b), 1.44-1.49 (m, 4H, H_a); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.9, 32.3, 21.0.

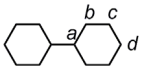
1,2-Diphenylethane



25

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and benzyl bromide (128 μL, 1 mmol) in DMF (2 mL) afforded 1,2-diphenylethane **25 (**76 mg, 95%) as a yellow oil which solidified on standing. ^{1}H NMR and ^{13}C NMR were consistent with published data.[31] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.32 (m, 4H, H_c), 7.17-7.23 (m, 6H, H_b and H_d), 2.93 (s, 4H, H_a); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 128.5, 128.4, 126.0, 38.0.

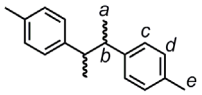
Bicyclohexyl



26

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and bromo-cyclohexane (133 μL, 1 mmol) in DMF (2 mL) afforded bicyclohexyl **26 (**89 mg, >99%) as a colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with published data.[32] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.75 (m, 10H), 0.88-1.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.5, 30.2, 26.9 (2xC).

2,3-Di-*p*-toluyl-butane

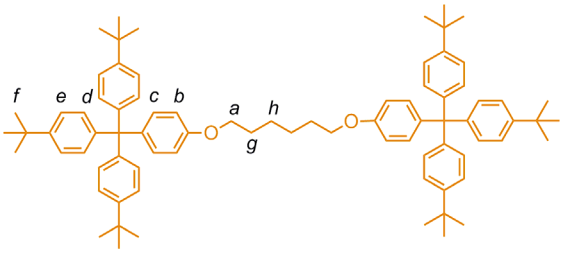


27

Following the general procedure with terpy (11.8 mg, 50 μmol), $NiCl_2$•$6H_2O$ (12.8 mg, 50 μmol), activated Zn (70 mg, 1 mmol) and 1-(1-bromoethyl)-4-methylbenzene (133 μL, 1 mmol) in DMF (2 mL) afforded 2,3-di-*p*-toluyl-butane **27 (**103 mg, 80%) as a pale yellow solid in a 1:1 mixture of the chiral and meso diastereoisomers as judged by ^{1}H NMR.[33]

meso-**27** – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (s, 8H, H_c + H_d), 2.68-2.79 (m, 2H, H_b), 2.27 (s, 6H, H_e), 0.96-1.03 (m, 6H, H_a).

chiral-**27** – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 7.9, 4H, H_d), 6.91-6.95 (m, 4H, H_c), 2.87-2.97 (m, 2H, H_b), 2.34 (s, 6H, H_e), 1.21-1.24 (m, 6H, H_a).



28

Following the general procedure with terpy (0.46 mg, 2 µmol), $NiCl_2$•$6H_2O$ (0.48 mg, 2 µmol), activated Zn (2.6 mg, 40 µmol) and stoppered bromide **2** (25 mg, 40 µmol) in DMF (0.5 mL) and THF (0.5 mL) afforded thread **28 (**22 mg, >99%) as a colorless solid. M.p >310 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.25 (m, 12H, H_e), 7.04-7.10 (m, 16H, H_c and H_d), 6.77-6.73 (m, 4H, H_b), 3.93 (t, 4H, J = 6.5, H_a), 1.75-1.83 (m, 4H, H_g), 1.49-1.54 (m, 4H, H_h), 1.26-1.32 (m, 54H, H_f); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 148.2, 144.1, 139.3, 132.2, 130.7, 124.0, 112.9, 67.6, 63.0, 34.2, 31.3, 29.3, 25.9; LREI-MS: *m/z* = 1091.5 $[MH]^+$; HREI-MS: *m/z* = 1090.755 $[M]^+$ (calcd. for $C_{80}H_{98}O_2$, 1090.756).

2.4.4 Crystal Data and Structure Refinement for 16

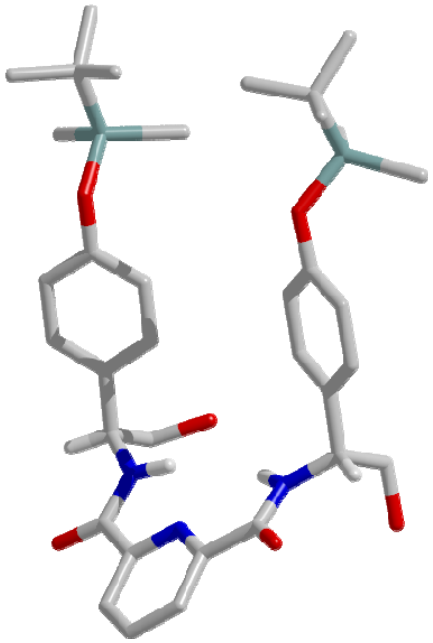


Figure 2.2. Crystal structure of the *meso* enantiomer of **16**. Carbon atoms are shown in light grey, nitrogen atoms blue, oxygen red, silicon green/grey, selected hydrogen atoms are shown in white.

Table 2.3. Crystal data and structure refinement for **16**.

Empirical formula	$C_{35}H_{52}N_3O_6Si_2$
Formula weight	674.98
Temperature	93(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1

Unit cell dimensions	a = 10.1290(6) Å α = 75.478(3)°.
	b = 18.6652(11) Å β = 88.638(3)°.
	c = 21.5360(13) Å γ = 78.940(3)°.
Volume	3867.0(4) $Å^3$
Z	4
Density (calculated)	1.159 Mg/m^3
Absorption coefficient	0.137 mm^{-1}
F(000)	1452
Crystal size	0.100 x 0.100 x 0.050 mm^3
Theta range for data collection	2.25 to 25.35°.
Index ranges	$-12 \leq h \leq 12$, $-19 \leq k \leq 22$, $-25 \leq l \leq 25$
Reflections collected	35807
Independent reflections	13692 [R(int) = 0.0510]
Completeness to theta = 25.00°	97.8 %
Absorption correction	Multiscan
Max. and min. transmission	1.0000 and 0.4884
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13692 / 8 / 892
Goodness-of-fit on F^2	1.051

Final R indices	[I>2sigma(I)] R1 = 0.0503, wR2 = 0.1215
R indices (all data)	R1 = 0.0591, wR2 = 0.1284
Extinction coefficient	0.0039(10)
Largest diff. peak and hole	0.822 and -0.695 e.Å^{-3}

2.5 References

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CHAPT. 3 | TWO AXLES THREADED USING A SINGLE TEMPLATE SITE: ACTIVE METAL TEMPLATE MACROBICYCLIC [3]ROTAXANES

Published as *'Two Axles Threaded Using a Single Template Site: Active Metal Template Macrobicyclic [3]Rotaxanes'* – Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315–320. Highlight: '*Templated Threading to [3]Rotaxanes'* – Swager, T. M.; Esser, B. *Synfacts* **2010**, *3*, 301.

Synopsis

Template approaches to rotaxanes normally require at least *n*-1 template sites to interlock *n* components. This Chapter describes the one-pot synthesis of [3]rotaxanes in which a single metal template site induces formation of axles through each cavity of a bicyclic macrocycle. Central to the approach is that the portion of the bicyclic molecule that is part of both rings acts as a ligand for a transition metal ion that mediates covalent bond formation through one or other cavity, depending on the ligand's orientation, making a mechanical bond. The bridging ligand can then rotate so that the transition metal can catalyze the formation of a second axle through the other macrocycle. Using this strategy with the Cu^{I}-catalyzed azide-alkyne cycloaddition (the CuAAC reaction) generates a [3]rotaxane with two identical axles in up to 86% yield. [3]Rotaxanes with two different axles threaded through the macrobicyclic rings can also be created using a single template site, either by having Cu^{I} sequentially form both mechanical bonds (via the CuAAC reaction) using different sets of building blocks for each axle, or by using two different reactions catalyzed by two different metal ions: a Pd^{II}-mediated alkyne homocoupling to assemble the first thread through one cavity, followed by a Cu^{I}-mediated CuAAC reaction to form the second axle through the other ring.

Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Dr. Vicki Ronaldson synthesized and grew X-ray quality crystals of **1a**.$PdCl_2$(MeCN), and synthesized macrocycle **1b**, and rotaxanes **5** and **6** jointly with the Author. Dr. Ronaldson and Dr. Stephen Goldup both had crucial input into the project design and wrote an initial draft of the published work which was refined together with the Author. Prof. Alexandra Slawin solved the crystal structure of **1a**.$PdCl_2$(MeCN).

3.1 Introduction

In recent years, template strategies have allowed increasingly elaborate structures featuring multiple mechanical bonds to be constructed.[1] Various examples of rotaxanes,[2] pseudorotaxanes,[3] catenanes[4] and other types[5] of molecular links with three or more mechanically bonds or components have been described. Systems with multiple mechanical bonds between components that are also covalently connected have also been prepared.[6-8] However, the vast majority of [*n*]rotaxanes with *n*>2 components consist of *n*-1 rings encircling a single thread (linear[2a,c,h,j,m-o,q] or branched[2b,e,j,k,l,p]), while rotaxanes consisting of multiple threads passing through rings are still rare.[2j,r,u,w] A feature common to almost[2n] all these synthetic strategies is that at least *n*-1 template sites is normally required to interlock *n* components. Here we report on the synthesis of [3]rotaxanes in which a single metal template site sequentially induces formation of an axle through each cavity of a bicyclic ring system. The methodology relies on 'active template'[9] rotaxane formation, in which a coordinated metal ion acts as both the template for the interlocked product and as a catalyst for promoting the formation of the crucial covalent bond that captures the threaded architecture. Active template synthesis has previously been used with a range of transition metal-catalyzed reactions to construct simple rotaxanes with macrocycles threaded onto a single axle. However, since the transition metal catalyst/template does not bind more strongly to the product than the starting material, it can in some cases[9a,9c-9e] turn over during the reaction. It seemed possible that by positioning the ligand at the junction between two macrocycle cavities the single template site might be able to direct active template reactions through each ring. Indeed, our investigation showed that two axles could be successfully threaded in this way, either be forming them using the same reaction (e.g. the Cu^{I}-catalyzed azide-alkyne cycloaddition – the CuAAC reaction[10]) or via two different reactions which utilize different transition metal ions (the CuAAC reaction and a Pd^{II}-catalyzed alkyne homocoupling[11]).

3.2 Results and Discussion

3.2.1 Macrobicyclic [3]Rotaxanes with Identical Axles

The synthesis of doubly-threaded [3]rotaxanes is significantly complicated by the sheer size of the 'stoppers' required to prevent de-threading of large rings.[2r,u,12] When contemplating how to achieve multiple threading with active template reactions that turn over, we were intrigued by the idea of incorporating the ligating site within a flexible bridging unit that bisected a large macrocycle into a bicyclic system. This should allow the ligand to orient the metal ion towards each cavity in turn, catalyzing covalent bond formation between appropriately derivatized building blocks through each cavity, producing [3]rotaxanes (Figure 3.1).

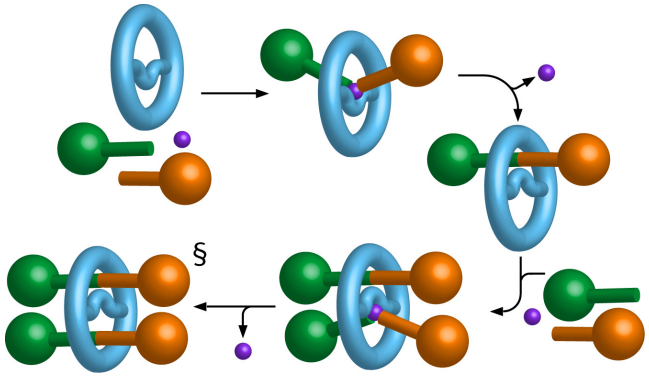


Figure 3.1. Active template synthesis of macrobicyclic [3]rotaxanes. The metal (purple) coordinates to the binding site that bridges the two macrocycles. The metal can then promote formation of a covalent bond through each cavity of the macrocycle in turn, generating a doubly-threaded [3]rotaxane. If the second thread forms significantly more slowly than the first (negative allostery), then the reaction can effectively be stopped at the intermediate [2]rotaxane stage and a different set of building blocks or even a different metal employed in a different active template reaction to form the second thread of the macrobicyclic [3]rotaxane. § If the threads being formed are not symmetrical through the mirror plane formed by the macrocycle, two different diastereoisomers (*syn*- and *anti*-arrangements of the threads) can be formed even though the threads themselves may be constitutionally identical.

Bicyclic macrocycle **1a** (Scheme 3.1 and Figure 3.2) incorporates a 2,6-disubstituted pyridine unit (previously employed as the ligating motif in the active template synthesis of simple [2]rotaxanes[9a,9c-9e]) in a bridge separating two identical cavities. CPK modeling studies indicated that with C_{14} alkyl chains (n = 2, Scheme 3.1) the rings should be large enough to accommodate a thread unit through each cavity while a tris(t-butyl)-substituted trityl group should be a sufficiently large stoppering group to prevent dethreading. The synthesis of **1a** was achieved in eight steps from the

commercially available dimethyl acetal of 2,6-dihydroxylbenzoic acid (*vide infra* – *Section 3.4*). Single crystals of a metal-coordinated **1a** complex suitable for X-ray analysis were obtained by slow cooling of a saturated solution of **1a**.$PdCl_2$(MeCN) in acetonitrile and the solid state structure (Figure 3.2) clearly shows the metal center orienting its chloride ligands so that they protrude through opposite sides of one of the macrocyclic cavities, as required by a rotaxane-forming active template mechanism.[9]

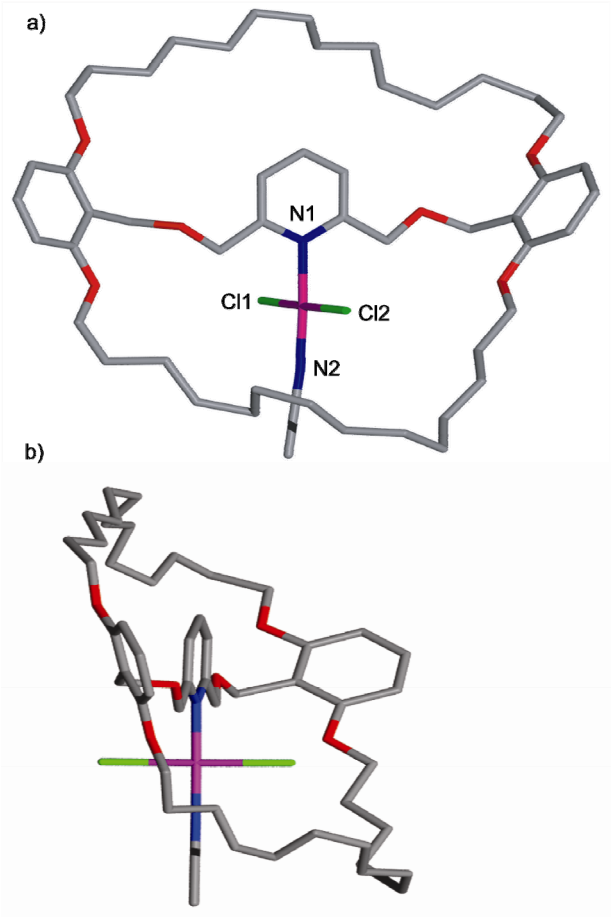


Figure 3.2. X-Ray crystal structure of **1a**.$PdCl_2$(MeCN), from a single crystal obtained by slow cooling of a saturated acetonitrile solution. Nitrogen atoms are shown in blue, oxygen atoms red, chlorine atoms green and palladium pink. Selected bond lengths [Å] and angles [°]: N1-Pd 2.02, N2-Pd 2.01, Cl1-Pd 2.28, Cl2-Pd 2.29, Cl1-Pd-Cl2 178.0. Structure viewed (a) in the plane of the pyridine ring and (b) to show the Cl1-Pd-Cl2 axis directed through one of the macrocyclic rings.

Carrying out the CuAAC reaction[9a,d] between alkyne **2** and azide **3** (5 molar equivalents of each) with a stoichiometric quantity of $CuPF_6$ and bicyclic macrocycle **1a** in 1,2-dichloroethane at 70 ºC over 24 h generated [2]rotaxane **5a**, which was

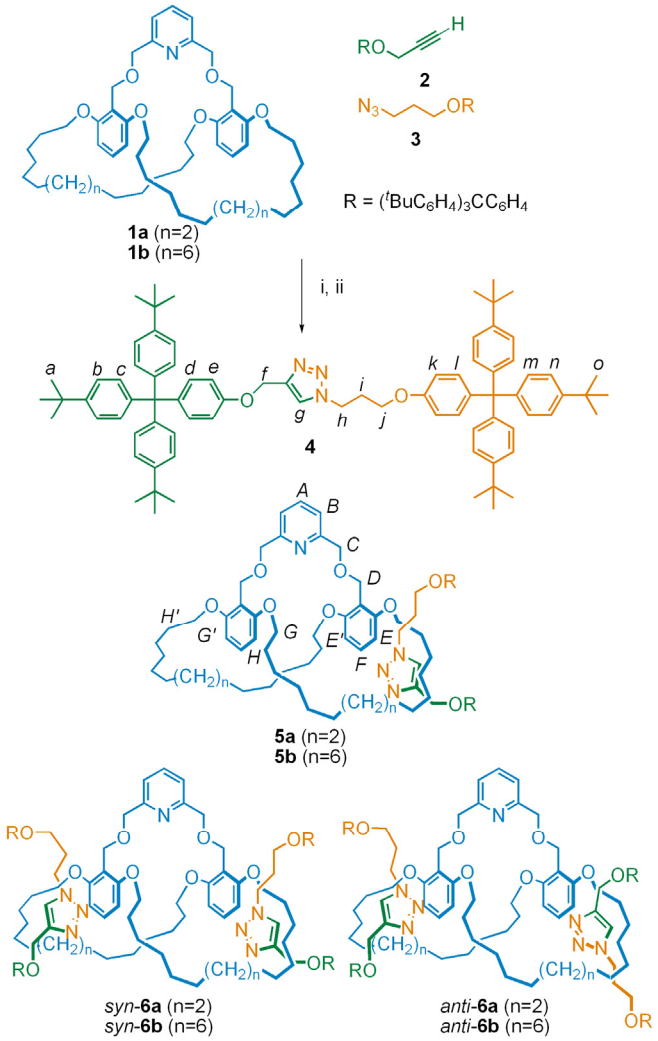
isolated in 41% yield after demetallation with a basic ethylenediaminetetraacetic acid-ammonia (EDTA-NH_3) solution (Scheme 3.1; Table 3.1, entry 1). However, despite using a large excess of the alkyne and azide building blocks, only a small amount (≤ 10%) of the accompanying [3]rotaxane **6a** was formed (Table 3.1, entry 1). It seemed that the low yield of [3]rotaxane **6a** might be a result of the second cavity becoming too congested to accommodate a threading reaction following formation of [2]rotaxane **5a**. We therefore synthesized macrocycle **1b** (*vide infra – Section 3.4*), which possessed an additional four methylene units in each of the macrocyclic rings. Pleasingly, treating this larger bicyclic structure (**1b**) with $CuPF_6$ and 5 molar equivalents (2.5 equivalents per macrocycle) of **2** and **3** furnished [2]rotaxane **5b** in 57% yield together with 41% of [3]rotaxane **6b**, a combined 98% yield of interlocked products (Table 3.1, entry 2). Following further addition of azide and alkyne (5 equiv. of each), the yield of [3]rotaxane **6b** was increased to 86% (Table 3.1, entry 3).

Table 3.1. Conversion of **1a** and **1b** to Macrobicyclic [2]-and [3]Rotaxanes (Scheme 3.1).

Entry	Macrocycle	Equiv.**2** and **3**	[2]Rotaxane yield [a]	[3]Rotaxane yield [a]
1[b]	**1a**	5.0	41% (**5a**)	≤10% (**6a**)[c]
2[a]	**1b**	5.0	57% (**5b**)	41% (**6b**)
3[d]	**1b**	10.0[e]	14% (**5b**)	86% (**6b**)

[a] Yields based on macrocycle **1**. [b] Reaction carried out over 24 h. [c] Yield determined by ^{1}H NMR. [d] Reaction carried out over 48 h. [e] 5 equiv. of each of **2** and **3** were introduced at the start of the reaction and again after 24 h.

Scheme 3.1. Synthesis of Macrobicyclic [2]- and [3]Rotaxanes via an Active Template CuAAC Reaction.[a]



[a]Reagents and conditions: (i) $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 ºC. (ii) EDTA, NH_3.

The structures of the [2]- and [3]rotaxanes were established unambiguously by mass spectrometry and NMR spectroscopy (*vide infra – Section 3.4*). Comparison of the ^{1}H NMR spectrum of [2]rotaxane **5b** (Figure 3.3b) with those of its non-interlocked components (macrocycle **1b** and thread **4**; figures 3.3a and 3.3d, respectively) shows upfield shifts of protons of the axle (H_f, H_h and H_k) and macrocycle (H_A, H_E and H_G) arising from these regions of the mechanically threaded components spending significant amounts of time face-on to aromatic rings. As only one of the two macrocycle cavities is threaded by an axle in [2]rotaxane **5b**, the bicyclic host is desymmetrized with respect to the parent compound **1b** (Figure 3.3a) and the ^{1}H NMR spectrum of the [2]rotaxane is correspondingly more complex (note, for

example, H_C, H_D and H_E in Figure 3.3b cf. Figure 3.3a). Penetration of axles through both macrocycle cavities in [3]rotaxane **6b** simplifies the ^{1}H NMR spectrum compared to that of [2]rotaxane **5b** and the H_E and H_G protons associated with each cavity produce coincident resonances (Figure 3.3c). This is in spite of the potential for stereoisomerism present in [3]rotaxane **6b**, which can exist as both *syn*- or *anti*-diastereomers depending on whether the axles are threaded in the same direction (*syn*-isomer) through the cavities or in opposite directions (*anti*-isomer), both of which would be expected to be produced in the [3]rotaxane-forming reaction (Scheme 3.1). Indeed, close examination (Figure 3.3e) of the signals corresponding to H_e and H_k reveals that they both appear as doubled sets of signals in [3]rotaxane **6b**, suggesting that both stereoisomers are indeed present in the [3]rotaxane reaction product but that they are almost indistinguishable by ^{1}H NMR.

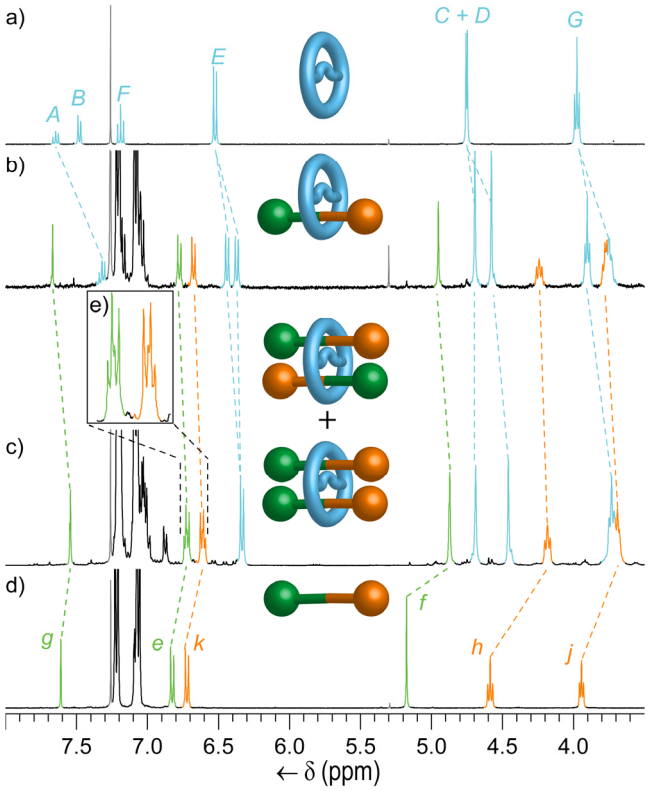


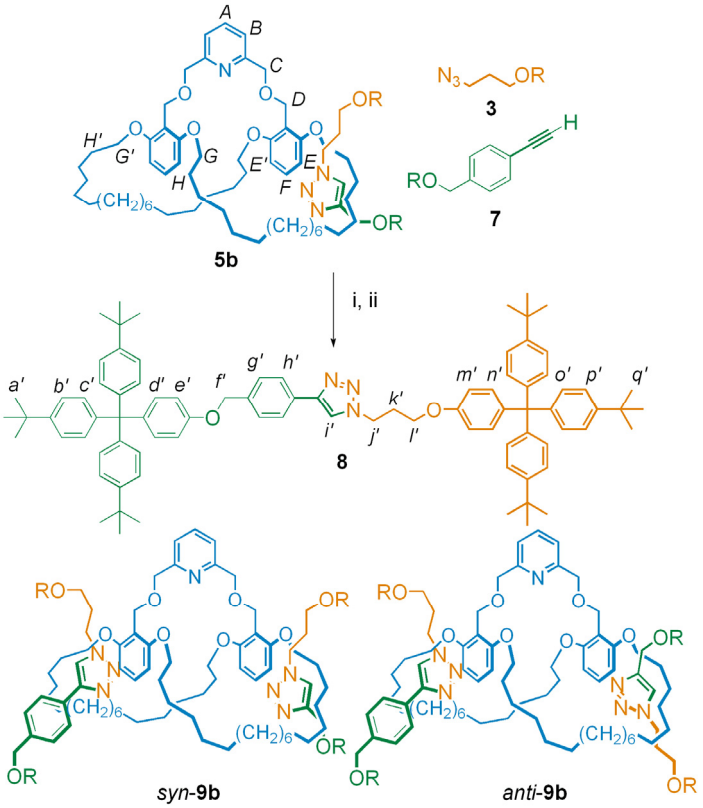
Figure 3.3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) macrocycle **1b**, b) [2]rotaxane **5b**, c) [3]rotaxane *syn*/*anti*-**6b**, d) non-interlocked thread **4** and e) expansion of the region showing resonances H_e and H_k in [3]rotaxane *syn*/*anti*-**6b**. The lettering corresponds to that shown in Scheme 3.1.

3.2.2 Macrobicyclic [3]Rotaxanes with Different Axles Assembled by Successive Active Template CuAAC Reactions

We next investigated whether the single template site could be used sequentially for the synthesis of [3]rotaxanes in which the thread components are non-identical. The slower formation of the axle through the second cavity (a form of negative allosteric regulation[13]) of **5b** allows the [2]rotaxane to be isolated in good yield (Table 3.1, entry 2). Carrying out a second active template CuAAC reaction on this [2]rotaxane intermediate utilizing alkyne **7** in place of alkyne **2** (Scheme 3.2) generated [3]rotaxane *syn*/*anti*-**9b,** with different triazole axles threaded through the two macrocycles, in 43% yield (Scheme 3.2). In the ^{1}H NMR spectrum of *syn*/*anti*-**9b** (Figure 3.4b) the formation of the second mechanical bond with a different (unsymmetrical) thread does not give a simplified spectrum of the bicyclic macrocycle component in the manner observed for **6b** (Figure 3.3c), with the signals

corresponding to H_E, for example, clearly arising from two chemically different sets of protons.

Scheme 3.2. Synthesis of a [3]Rotaxane with Two Different Triazole Threads via Successive CuAAC Active Template Reactions [a]



[a]Reagents and conditions: (i) $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 ºC. (ii) EDTA, NH_3. 43%.

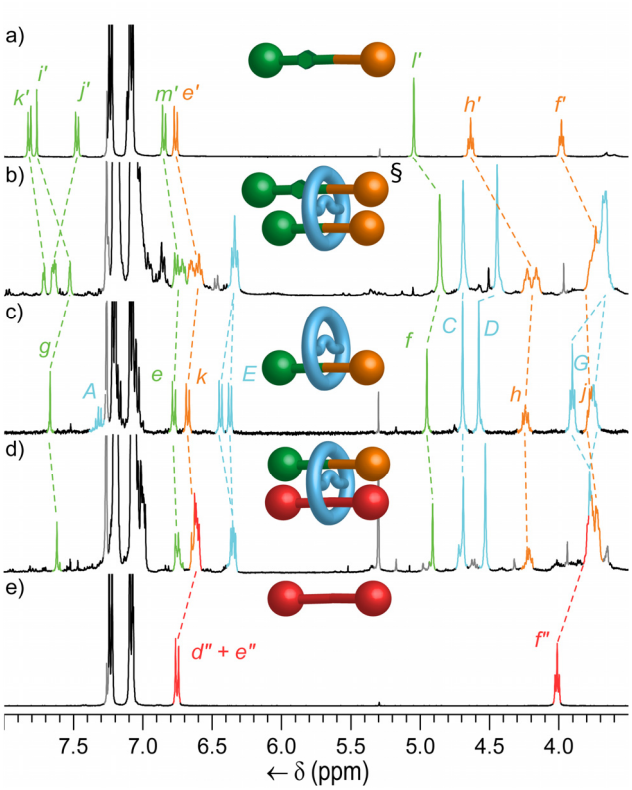


Figure 3.4. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) non-interlocked thread **8**, b) mixed-triazole-thread [3]rotaxane *syn*/*anti*-**9b**, c) [2]rotaxane **5b**, d) bis-acetylene-thread-triazole-thread [3]rotaxane **10b** and e) non-interlocked thread **11**. The lettering corresponds to that shown in Schemes 3.2 and 3.3. § Mixture of *syn*- and *anti*-isomers.

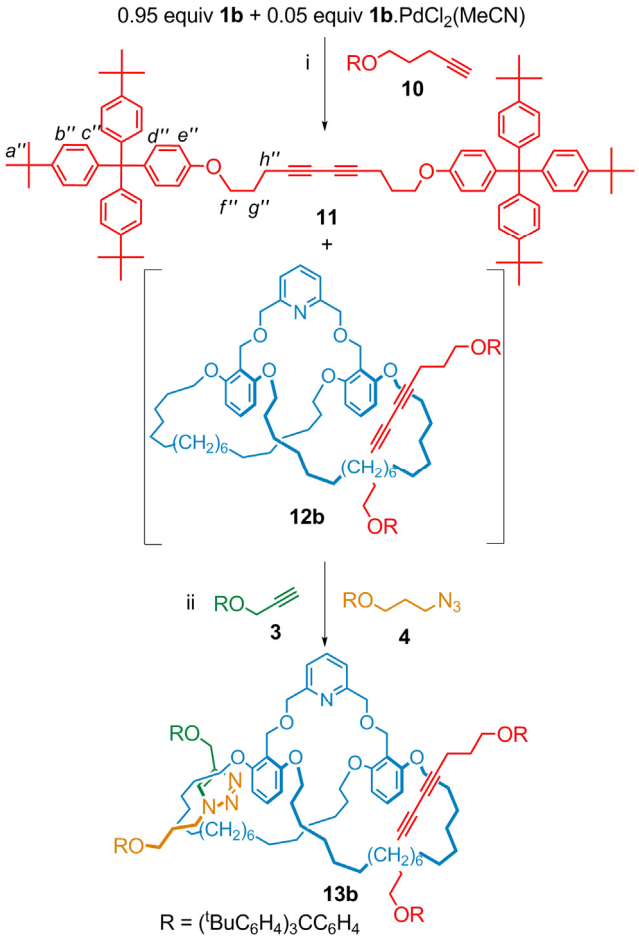
3.2.3 Macrobicyclic [3]Rotaxanes with Different Axles Assembled Using Two Different Chemical Reactions

Finally, we attempted the synthesis of [3]rotaxanes using two different active template reactions (catalyzed by different transition metals) to sequentially assemble the two threads via the bridging template site. A Pd^{II}-catalyzed alkyne homocoupling[11] was selected as the second axle-forming reaction as it has previously been successfully used[9e] to assemble simple [2]rotaxanes via active template syntheses using a 2,6-disubstituted pyridine unit as the ligating group. However, when [2]rotaxane **5b** was subjected to these reaction conditions with alkyne **10**, no [3]rotaxane was detected in the reaction mixture. We reasoned that this could be because the triazole ring of the already threaded axle in **5b** could potentially coordinate[14] to the Pd^{II} and inhibit the second active template reaction. We therefore tried switching the order in which the axles were formed, attempting to form the threaded axle from the active template Pd^{II}-alkyne homocoupling first and then

applying the Cu^{I}-catalyzed alkyne-azide cycloaddition with fresh alkyne and azide building blocks (Scheme 3.3).

The reaction sequence was carried out without purification of the intermediate [2]rotaxane (**12b**). Bicyclic macrocycle **1b** was subjected to the Pd^{II}-mediated alkyne homocoupling conditions (5 mol% **1b**.$PdCl_2$(MeCN), 30 equiv. **10**, iPr_2NH, CuI, I_2, benzene) with stoppered alkyne **10**. After 5 days, all the alkyne had been consumed although ^{1}H NMR suggested only ~10% conversion to the [2]rotaxane, **12b**, which was not isolated. The solution was extracted with EDTA-NH_3 and filtered to remove residual Pd and then the reaction vessel charged with azide and alkyne building blocks **3** and **4** and the $CuPF_6$ catalyst, and subjected to the CuAAC reaction conditions. [3]Rotaxane **13b**, with both bis-acetylene and triazole threads was isolated in 4% yield over these two synthetic steps (Scheme 3.3). Whilst the yield is certainly modest (largely the result of the Pd^{II}-promoted homocoupling being so poor, the second axle is threaded through the [2]rotaxane intermediate **12b** in ~40% yield), it nonetheless demonstrates that it is possible to direct two different metal-catalyzed reactions sequentially through different (chemically identical) cavities through the action of one bridging ligating group. As with the other rotaxanes reported here, [3]rotaxane **13b** was unambiguously characterized by NMR spectroscopy and mass spectrometry (*vide infra – Section 3.4*). The ^{1}H NMR of [3]rotaxane **13b** (Figure 3.4d) is not complicated by the diasteroisomerism present in *syn/anti*-**6b** and *syn/anti*-**9b** since the bis-acetylene thread component is symmetrical.

Scheme 3.3. Synthesis of a [3]Rotaxane with Bis-Acetylene and Triazole Threads via Sequential Active Template Reactions.[a]



[a]Reagents and conditions: (i) **10** (30 eq.), diisopropylamine (10 eq.), CuI (2 eq.), I_2 (0.5 eq.), rt, benzene. (ii) 1. Alkyne **3** (5 eq.), azide **4** (5 eq.), $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 ºC, 2. EDTA, NH_3. 4% yield over both mechanical bond-forming steps: ~10% for the first (formation of **12b**); ~40% for the second (formation of **13b**).

3.3 Conclusions

We have demonstrated that it is possible for a ligand located at the junction of two macrocycles to successively promote covalent bond forming reactions through each cavity of a bicyclic structure, a coordinated transition metal ion simultaneously acting as a catalyst and a template for mechanical bond formation each time. Using the CuAAC reaction of azide and alkyne building blocks, the formation of [3]rotaxanes is remarkably effective, proceeding in up to 86% yield (>94% per axle). It is even possible to form two mechanical bonds with different axles, although this is less efficient (65% per axle using the CuAAC reaction twice), particularly when

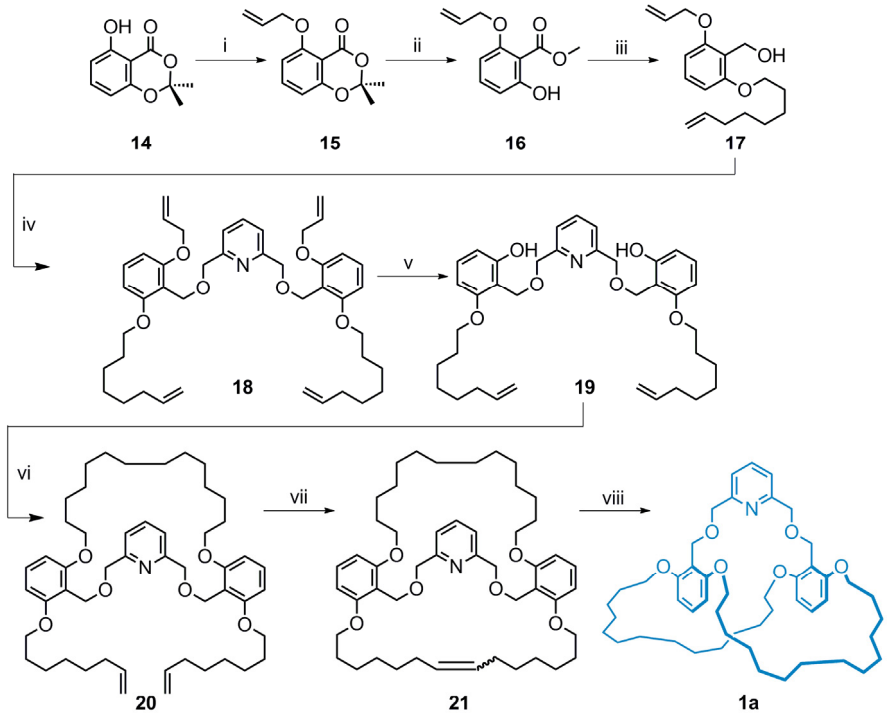
employing chemical reactions catalyzed by different metal ions (~10% and ~40%, respectively, for a Pd^{II}-catalyzed alkyne homocoupling followed by a Cu^{I}-catalyzed CuAAC reaction). The ability to form multiple mechanical bonds via a single template site is a potentially significant addition to the toolbox for interlocked molecule assembly. It may prove useful for constructing heterocircuit Borromean rings,[15] for example, (through the use of cleavable bridging ligands) and other currently inaccessible higher order links that require the threading of multiple different axles through large rings.

3.4 Experimental Details

3.4.1 Synthesis of Macrobicycles 1a and 1b

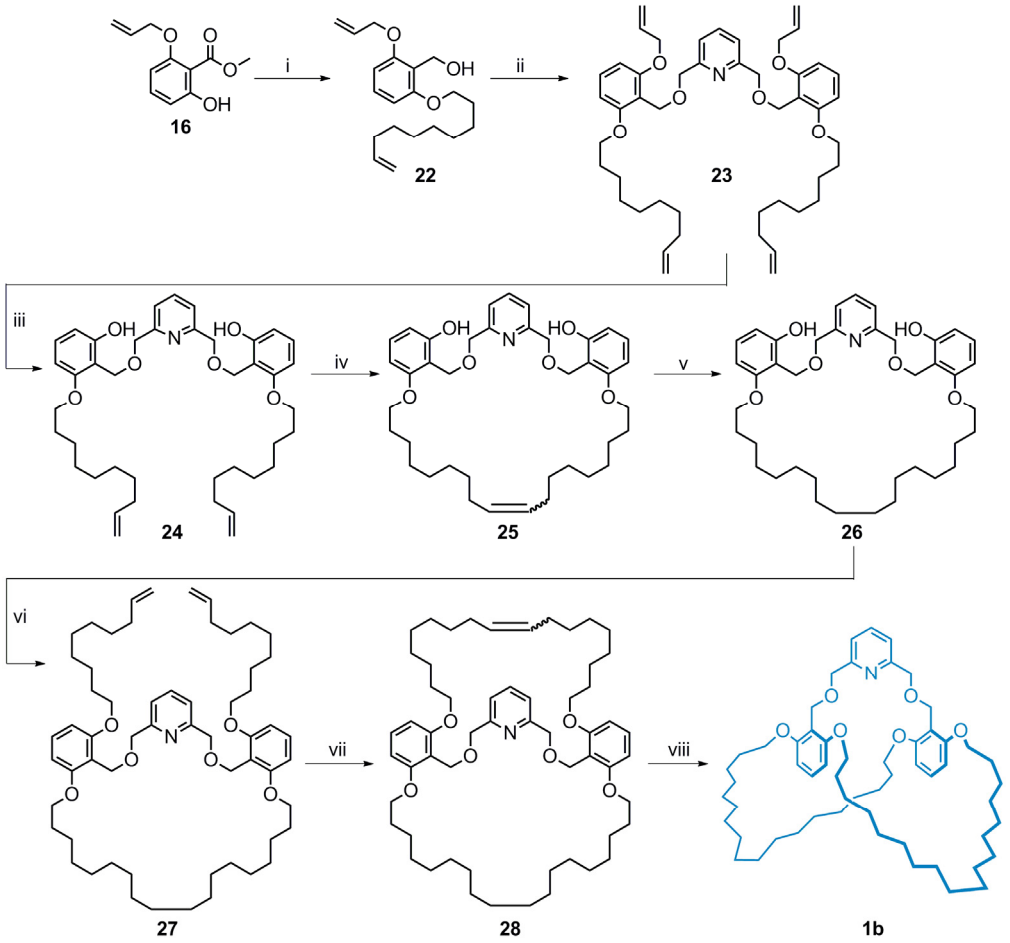
2,6-Bis(bromomethyl) pyridine[16] and 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin[17] were prepared following literature procedures. Tetradecane-1,14-ditosylate was prepared in 3 steps, from the diacid, following literature procedures.[18]

Scheme 3.4. Synthesis of bicyclic macrocycle **1a**.



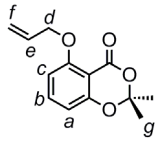
Reagents and conditions: (i) allyl bromide, NaI, K_2CO_3, butanone, Δ, 75%; (ii) K_2CO_3, MeOH, 86%; (iii) 1. 8-bromooctene, K_2CO_3, butanone, Δ, 2. $LiAlH_4$, THF, 0 ºC→rt, 62%; (iv) NaH, 2,6-bis(bromomethyl)pyridine, DMF, 0 ºC→rt, 60%; (v) $Pd(PPh_3)_4$, aniline, THF, 30 ºC, 71%; (vi) tetradecane-1,14-ditosylate, K_2CO_3, DMF, 100 ºC, 60%; (vii) $PhCH{=}Ru(PCy_3)_2Cl_2$, CH_2Cl_2, 64%; (viii) Pd/C, $H_{2\,(g)}$, THF, 96%.

Scheme 3.5. Synthesis of bicyclic macrocycle **1b**.



Reagents and conditions: (i) 1. 10-bromodecene, K_2CO_3, butanone, Δ, 2. $LiAlH_4$, THF, 0 ºC→rt, 52%; (ii) NaH, 2,6-bis(bromomethyl)pyridine, DMF, 0 ºC→rt, 57%; (iii) $Pd(PPh_3)_4$, aniline, THF, 30 ºC, 96%; (iv) $PhCH=Ru(PCy_3)_2Cl_2$, CH_2Cl_2, 47%; (v) Pd/C, $H_{2\ (g)}$, THF, >99%; (vi) 10-bromodecene, K_2CO_3, butanone, Δ, 56%, (vii) $PhCH=Ru(PCy_3)_2Cl_2$, CH_2Cl_2, 83%; (viii) Pd/C, $H_{2\ (g)}$, THF, 98%.

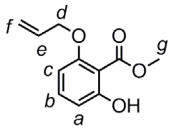
5-Allyloxy-2,2-dimethyl-benzo[1,3]dioxin-4-one



15

Allyl bromide (8.9 mL, 102.3 mmol) and NaI (cat.) were added to a solution of 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin (13.24 g, 68.2 mmol) and K_2CO_3 (47.13 g, 341 mmol) in butanone (200 mL) and the reaction mixture heated at reflux for 18 h. The reaction mixture was allowed to cool to rt and CH_2Cl_2 (100 mL) and water (100 mL) were added. The phases were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was purified by column chromatography (petrol-CH_2Cl_2, 2:1) to give acetonide **15**[17] (12.03 g, 75%) as a colorless solid. M.p 45-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4 (t, 1H, J = 8.42, H_b), 6.59 (d, 1H, J = 8.5, H_a or H_c), 6.53 (dd, 1H, J = 8.2, 0.5, H_a or H_c), 6.12-6.02 (m, 1H, H_e), 5.60-5.53 (m, 1H, H_f-*trans*), 5.34-5.29 (m, 1H, H_f-*cis*), 4.67 (dt, 2H, J_d = 4.8, J_t = 1.6, H_d), 1.69 (s, 6H, H_g); LRFAB-MS (3-NOBA matrix): *m/z* = 234 [M].$^+$

2-(allyloxy)-6-hydroxybenzoic acid

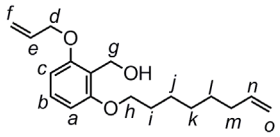


16

Acetonide **15** (4.00 g, 17.0 mmol) was dissolved in MeOH (100 mL) and K_2CO_3 (23.0 g, 170 mmol) was added. No inert atmosphere was required. The reaction mixture was allowed to stir at rt for 18 h. H_2O (300 mL) and CH_2Cl_2 (200 mL) were added and the phases separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 x 100 mL) and the combined extracts washed with brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give methyl ester **16**[19] (3.06 g, 86%) as a

pale orange solid which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.52 (s, 1H, OH), 7.31 (t, 1H, *J* = 8.4, H_b), 6.60 (dd, 1H, *J* = 8.3, 0.7, H_a or H_c), 6.40 (d, 1H, *J* = 8.3, H_a or H_c), 6.10-6.01 (m, 1H, H_e), 5.53 (dd, 1H, *J* = 17.2, 1.7, H_f-*trans*), 5.31 (dd, 1H, *J* = 10.7, 1.6, H_f-*cis*), 4.56 (dt, 1H, J_d = 4.3, J_t = 1.6, H_d), 4.00 (s, 3H, H_g).

(2-(allyloxy)-6-(oct-7-enyloxy)phenyl)methanol

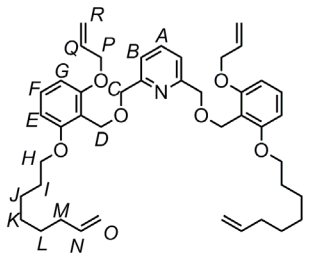


17

8-Bromooctene (4.40 mL, 26.0 mmol) was added to a solution of **16** (4.55 g, 22.0 mmol) and K_2CO_3 (15.0 g, 109 mmol) in butanone (150 mL) and the reaction mixture was heated at reflux for 18 h. Volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL). The phases were separated and the aqueous phase was further extracted with CH_2Cl_2 (100 mL). The combined organic extraxcts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was added to a suspension of $LiAlH_4$ (2.00 g, 43.4 mmol) in THF (200 mL) at 0 ºC and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was then cooled to 0 ºC and 10 M aqueous NaOH was added slowly, with vigorous stirring, until a colorless precipitate formed. This finely divided precipitate was removed by suction filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (petrol-EtOAc, 10:1) to give alcohol **17** (3.94 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, 1H, *J* = 8.3, H_b), 6.54 (d, 1H, *J* = 8.3, H_a or H_c), 6.53 (d, 1H, *J* = 8.3, H_a or H_c), 6.11-6.01 (m, 1H, H_e), 5.87-5.76 (m, 1H, H_n), 5.41 (ddt, 1H, J_d = 17.3, 1.6, J_t = 1.6, H_f-*trans*), 5.28 (ddt, 1H, J_d = 10.6, 1.4, J_t = 1.3, H_f-*cis*), 5.00 (ddt, 1H, J_d = 17.1, 1.9, J_t = 1.6, H_o-*trans*), 4.95-4.91 (m, 1H, H_o-*cis*), 4.84 (s, 2H, H_g), 4.56 (dt, 2H, J_d = 5.2, J_t = 1.5, H_d), 3.99 (t, 2H, *J* = 6.5, H_h), 2.62 (br-s, 1H, OH), 2.08-2.01 (m, 2H, H_m), 1.85-1.75 (m, 2H, H_i), 1.50-1.27 (m, 6H, H_j, H_k, H_l); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8,

157.2, 138.8, 133.0, 128.8, 117.3, 114.2, 104.8, 104.7, 69.1, 68.3, 55.0, 33.6, 29.1, 28.7 (Cx3), 25.9; LRESI-MS: *m/z* = 308 $[M+NH_4]^+$; HRESI-MS: *m/z* = 308.22244 $[M+NH_4]^+$ (calc. for $C_{18}H_{30}O_3N_1$ 308.22202).

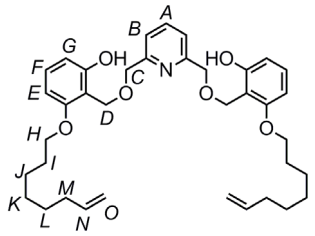
2,6-bis((2-(allyloxy)-6-(oct-7-enyloxy)benzyloxy)methyl)pyridine



18

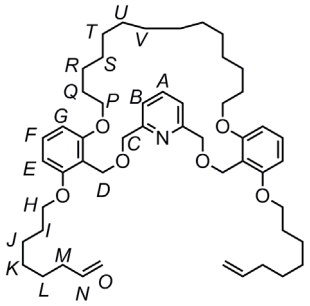
NaH (1.40 g, 58.4 mmol) was added to a solution of alcohol **17** (5.65 g, 19.5 mmol) in DMF (150 mL) at 0 ºC. After 30 min 2,6-bis(bromomethyl)pyridine[16] (2.2 g, 7.8 mmol) was added and the reaction mixture was allowed to warm from 0 ºC to rt and stirred for 18 h. A small amount of H_2O was added slowly to quench excess NaH, and the solvent was removed under reduced pressure. Column chromatography of the resulting residue (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2-EtOAc, 50:1) gave **18** (3.22 g, 60%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (t, 1H, *J* = 7.7, H_A), 7.44 (d, 2H, *J* = 7.7, H_B), 7.19 (t, 2H, *J* = 8.3, H_F), 6.53 (d, 2H, *J* = 8.3, H_E or H_G), 6.52 (d, 2H, *J* = 8.3, H_E or H_G), 6.12-6.01 (m, 2H, H_Q), 5.87-5.76 (m, 2H, H_N), 5.39 (ddt, 2H, J_d = 17.2, 1.6, J_t = 1.6, H_R-*trans*), 5.24 (ddt, 2H, J_d = 10.6, 1.5, J_t = 1.4, H_R-*cis*), 4.98 (dd, 2H, J_d = 17.1, 2.0, J_t = 1.6, H_O-*trans*), 4.92 (*app*-d, 2H, J_d = 10.2, H_O-*cis*), 4.77 (s, 4H, H_C), 4.70 (s, 4H, H_D), 4.56 (dt, 4H, J_d = 5.1, J_t = 1.5, H_P), 3.97 (t, 4H, *J* = 6.5, H_H), 2.02-1.93 (m, 4H, H_M), 1.79-1.70 (m, 4H, H_I), 1.42-1.19 (m, 12H, H_J, H_K, H_L); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.7, 158.5, 139.0, 136.7, 133.5, 129.7, 129.6, 119.4, 117.0, 114.9, 114.3, 105.0, 104.9, 73.2, 69.3, 68.5, 61.4, 33.7, 29.3, 28.8, 25.9; LRESI-MS: *m/z* = 685 $[M+H]^+$; HRESI-MS: *m/z* = 684.42586 (calc. for $C_{43}H_{58}NO_6$ 684.42533).

2-(((6-((2-hydroxy-6-(oct-7-enyloxy)benzyloxy)methyl)pyridin-2-yl)methoxy)methyl)-3-(oct-7-enyloxy)phenol



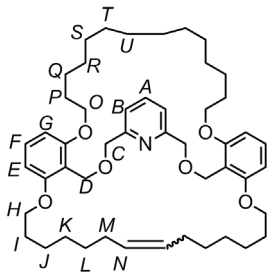
19

$Pd(PPh_3)_4$ (9.20 mg, 0.08 mmol) was added to a solution of bis-allyl-protected diphenol **18** (350 mg, 0.51 mmol) and aniline (0.2 mL, 2.04 mmol) in THF (2 mL). The reaction mixture was stirred at 30 ºC for 4 h. H_2O (10 mL) and 3:1 $CHCl_3$-IPA (10 mL) were added and the phases separated. The aqueous phase was further extracted with 3:1 $CHCl_3$-IPA (2 x 20 mL) and the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL) and concentrated under reduced pressure. Column chromatography of the resulting residue (gradient elution: 1. petrol, 2. petrol-EtOAc, 10:1) gave diphenol **19** (230 mg, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD, 3:1): δ = 7.58 (t, 1H, J = 7.7, H_A), 7.22 (d, 2H, J = 7.7, H_B), 6.95 (t, 2H, J = 8.2, H_F), 6.35 (d, 2H, J = 7.7, H_E or H_G), 6.26 (d, 2H, J = 8.2, H_E or H_G), 5.69-5.58 (m, 2H, H_N), 4.82 (ddt, 2H, J_d = 17.1, 2.0, J_t = 1.6, H_O-*trans*), 4.76 (*app*-d, 2H, J_d = 10.2, H_O-*cis*), 4.69 (s, 4H, H_C), 4.62 (s, 4H, H_D), 3.78 (t, 4H, J = 6.5, H_H), 1.92-1.84 (m, 4H, H_M), 1.65-1.54 (m. 4H, H_I), 1.33-1.10 (m, 12H, H_J, H_K, H_L); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD, 3:1): δ = 157.7, 157.3, 157.1, 138.6, 137.5, 129.3, 120.0, 113.8, 111.2, 108.6, 102.7, 71.5, 68.0, 62.9, 33.3, 28.8 (Cx2), 28.4, 25.6; LRESI-MS: *m/z* = 604 $[M+H]^+$; HRESI-MS: *m/z* = 604.36277 $[M+H]^+$ (calc. for $C_{37}H_{50}NO_6$ 604.36326).



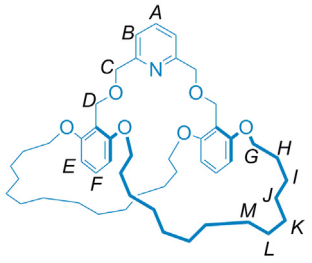
20

Tetradecane-1,14-ditosylate[18] (550 mg, 1.02 mmol) was added to a solution of diphenol **19** (616 mg, 1.02 mmol) and K_2CO_3 (1.41 g, 10.2 mmol) in DMF (2 L) and the reaction mixture was heated at 100 ºC for 18 h. Volatiles were removed under reduced pressure and 3:1 $CHCl_3$-IPA (200 mL) and H_2O (200 mL) were added and the phases separated. The aqueous phase was extracted with 3:1 $CHCl_3$-IPA (2 x 100 mL) and the combined organic phases were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the resulting residue (petrol-EtOAc, 10:1) gave compound **20** (814 mg, 60%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (t, 1H, J = 7.7, H_A), 7.46 (d, 2H, J = 7.7, H_B), 7.19 (t, 2H, J = 8.3, H_F), 6.51 (d, 4H, J = 8.36, H_E and H_G), 5.85-5.75 (m, 2H, H_N), 4.98 (ddt, 2H, J_d = 17.1, 1.8, J_t = 1.6, H_O-*trans*), 4.92 (*app*-d, 2H, J_d = 10.1, H_O-*cis*), 4.75 (s, 4H, H_C), 4.73 (s, 4H, H_D), 4.01-3.95 (m, 8H, H_H and H_P), 2.07-2.03 (m, 4H, H_M), 1.84-1.74 (m, 8H, H_I and H_Q), 1.64-1.61 (m, 4H, H_L), 1.54-1.21 (m, 28H, H_J, H_K, H_R. H_S, H_T, H_U, H_V); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.9, 158.8, 139.0, 136.6, 129.6, 119.2, 114.6, 114.3, 104.5, 104.4, 73.5, 68.5, 68.4, 61.6, 33.7, 29.4, 29.3 (Cx2), 29.2 (Cx3), 28.8 (Cx2), 26.2, 25.9; LRESI-MS: *m/z* = 799 $[M+H]^+$; HRESI-MS: *m/z* = 798.356672 $[M+H]^+$ (calc. for $C_{51}H_{76}O_6N$ 798.56471).



21

Dialkene **20** (470 mg, 0.59 mmol) in degassed CH_2Cl_2 (25 mL) was added to a solution of Grubbs' 1st generation catalyst ($PhCH=Ru(PCy_3)_2Cl_2$, 49 mg, 59.0 µmol) in degassed CH_2Cl_2 (600 mL) and the reaction mixture was allowed to stir at rt for 18 h. Ethyl vinyl ether (3 mL) was added and solution concentrated under reduced pressure. Column chromatography of the resulting residue (CH_2Cl_2) gave **21** (290 mg, 64%) as a colorless solid. M.p. 114-117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, 1H, *J* = 7.7, H_A), 7.47 (d, 2H, *J* = 7.7, H_B), 7.18 (t, 2H, *J* = 8.3, H_F), 6.52 (d, 4H, *J* = 8.4, H_G and H_E), 4.43-4.41 (m, 1.8H, H_N-*major*), 5.39-5.37 (m, 0.2H, H_N-*minor*), 4.75 (s, 4H, H_C), 4.74 (s, 4H, H_D), 3.98 (t, 8H, *J* = 5.9, H_H and H_O), 2.05-1.95 (m, 4H, H_M), 1.85-1.77 (m, 8H, H_I and H_P), 1.58-1.50 (m, 8H, H_J and H_L), 1.36-1.28 (m, 12H, H_K, H_Q and H_R), 1.28-1.19 (m, 12H, H_S, H_T, H_U); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.9, 158.8, 136.6, 130.3, 129.6, 119.1, 114.4, 104.3 (Cx2), 73.7, 68.4 (Cx2), 61.7, 32.5, 29.5 (Cx4), 29.4, 29.2 (Cx2), 29.1, 26.4, 26.3; LRESI-MS: *m/z* = 770 $[M]^+$; HRESI-MS: *m/z* = 770.53396 (calc. for $C_{49}H_{72}O_6N$ 770.53542).

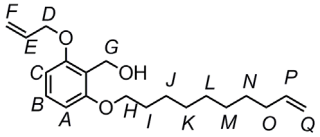


1a

Pd/C (27.0 mg of a 10% w/w dispersion) was added to a solution of **21** (270 mg, 0.35 mmol) in THF (25 mL). The reaction mixture was allowed to stir under an atmosphere of $H_{2\ (g)}$ for 5 h. The reaction mixture was filtered through celite and

concentrated under reduced pressure to give macrocycle **1a** (260 mg, 96%) as a colorless solid. M.p. 85-88 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (t, 1H, *J* = 7.7, H_A), 7.47 (d, 2H, *J* = 7.7, H_B), 7.19 (t, 2H, *J* = 8.3, H_F), 6.52 (d, 4H, *J* = 8.4, H_E), 4.76 (s, 4H, H_C), 4.75 (s, 4H, H_D), 3.98 (t, 8H, *J* = 6.0, H_G), 1.85-1.76 (m, 8H, H_H), 1.57-1.49 (m, 8H, H_I), 1.41-1.25 (m, 32H, H_J, H_K, H_L, H_M); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.9, 136.6, 129.6, 119.0, 114.5, 104.3, 73.8, 68.4, 61.8, 29.5, 29.4, 29.3, 29.2 (Cx2), 26.3; LRESI-MS: *m/z* = 773 $[M+H]^+$; HRESI-MS: *m/z* = 772.55340 $[M+H]^+$ (calc. for $C_{49}H_{74}O_6N$ 772.55107).

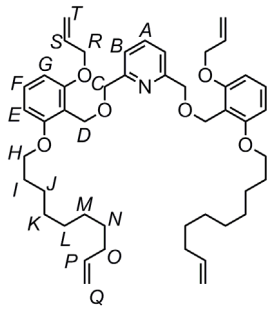
(2-(allyloxy)-6-(dec-9-enyloxy)phenyl)methanol



22

Phenol **16** (2.58 g, 12.4 mmol), K_2CO_3 (8.60 g, 62.0 mmol) and 1,10-dibromodecene (3.0 mL, 14.9 mmol) were reacted and the resulting residue treated with $LiAlH_4$, as described for **17**, to give **22** (2.06 g, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, 1H, *J* = 8.3, H_B), 6.54 (d, 1H, *J* = 8.3, H_A or H_C), 6.53 (d, 1H, *J* = 8.3, H_A or H_C), 6.12-6.01 (m, 1H, H_E), 5.87-5.76 (m, 1H, H_P), 5.41 (ddt, 1H, J_d = 17.3, 1.6, J_t = 1.6, H_F-*trans*), 5.28 (ddt, 1H, J_d = 10.6, 1.4, J_t = 1.4, H_F-*cis*), 5.00 (*app*-d, 1H, J_d = 17.13, H_Q-*trans*), 4.93 (*app*-d, 1H, J_d = 10.2, H_Q-*cis*), 4.84 (s, 2H, H_G), 4.56 (dt, 2H, J_d = 5.2, J_t = 1.5, H_D), 3.99 (t, 2H, *J* = 6.5, H_H), 2.62 (br-s, 1H, OH), 2.08-2.01 (m, 2H, H_O), 1.85-1.75 (m, 2H, H_I), 1.50-1.26 (m, 10H, H_J, H_K, H_L, H_M, H_N); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 157.2, 139.1, 133.1, 128.9, 117.5, 117.4, 114.1, 104.9, 104.8, 69.2, 68.4, 55.1, 33.7, 29.3, 29.3 (Cx2), 29.0, 28.8, 26.1; LRSEI-MS: *m/z* = 336 $[M+NH_4]^+$; HRESI-MS: *m/z* = 336.25301 $[M+NH_4]^+$ (calc. for $C_{20}H_{34}O_3N$ 336.25332).

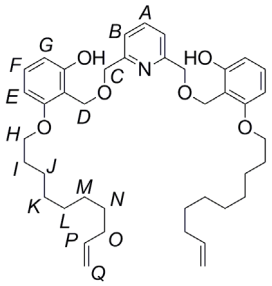
2,6-bis((2-(allyloxy)-6-(dec-9-enyloxy)benzyloxy)methyl)pyridine



23

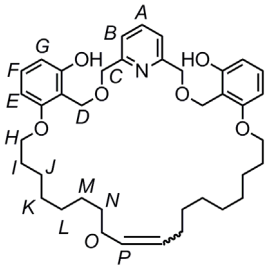
Alcohol **22** (649 mg, 2.04 mmol), 2,6-bis(bromomethyl)pyridine[16] (246 mg, 0.93 mmol) and NaH (150 mg, 6.14 mmol) were reacted as described for **18**. Column chromatography (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2-EtOAc 50:1) gave **23** (390 mg, 57%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (t, 1H, J = 7.7, H_A), 7.44 (d, 2H, J = 7.7, H_B), 7.18 (t, 2H, J= 8.3, H_F), 6.54 (d, 2H, J = 6.1, H_E or H_G), 6.52 (d, 2H, J = 6.3, H_E or H_G), 6.08-5.99 (m, 2H, H_S), 5.85-5.75 (m, 2H, H_P), 5.41 (ddt, 2H, J_d = 17.3, 1.6, J_t = 1.6, H_T-*trans*), 5.24 (ddt, 2H, J_d = 10.6, 1.5, J_t = 1.4, H_T-*cis*), 4.98 (ddt, 2H, J_d = 17.1, 2.1, J_t = 1.6, H_Q-*trans*), 4.92 (*app*-d, 2H, J_d= 10.2, H_Q-*cis*), 4.77 (s, 4H, H_C), 4.71 (s, 4H, H_D), 4.56 (dt, 4H, J_d = 5.1, J_t = 1.5, H_R), 3.98 (t, 4H, J= 6.5, H_H), 2.05-2.00 (m, 4H, H_O), 1.81-1.74 (m, 4H, H_I), 1.47-1.23 (m, 20H, H_I, H_J, H_K, H_L, H_M); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 158.6, 158.4, 139.2, 136.6, 133.4, 129.6, 119.3, 117.0, 114.7, 114.1, 104.8 (Cx2), 73.1, 69.2, 68.4, 61.3, 33.7, 29.4, 29.3, 29.2, 29.0, 28.8, 26.0; LRESI-MS: *m/z* = 740 $[M+H]^+$; HRESI-MS: *m/z* = 740.48847 (calc. for $C_{47}H_{66}O_6N$ 740.48847).

2-(((6-((2-(dec-9-enyloxy)-6-hydroxybenzyloxy)methyl)pyridin-2-yl)methoxy)methyl)-3-(dec-9-enyloxy)phenol



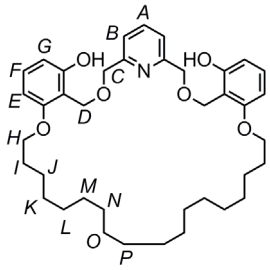
24

Bis-allyl protected diphenol **23** (1.45 g, 1.96 mmol) was treated with $Pd(PPh_3)_4$ (0.34 g, 0.29 mmol) and aniline (0.70 mL, 7.84 mmol) as described for **19**. Column chromatography (gradient elution: 1. petrol-EtOAc, 10:1, 2. petrol-EtOAc, 5:1) gave diphenol **24** (1.24 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD, 3:1): δ = 7.54 (t, 1H, J = 7.8, H_A), 7.20 (d, 2H, J = 7.7, H_B), 6.91 (t, 2H, J = 8.2, H_F), 6.31 (d, 2H, J = 8.1, H_E or H_G), 6.23 (d, 2H, J = 8.2, H_E or H_G), 5.65-5.55 (m, 2H, H_P), 4.78 (ddt, 2H, J_d = 17.1, 1.7, H_Q-*trans*), 4.72 (*app*-d, 2H, J_d = 10.2, H_Q-*cis*), 4.65 (s, 4H, H_C), 4.58 (s, 4H, H_D), 3.75 (t, 4H, J = 6.5, H_H), 1.85-1.81 (m, 4H, H_O), 1.61-1.54 (m, 4H, H_I), 1.27-1.09 (m, 20H, H_J, H_K, H_L, H_M, H_N); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD, 3:1): δ = 157.8, 157.3, 157.1, 138.7, 137.5, 129.3, 119.9, 113.6, 111.3, 108.5, 102.7, 71.4, 68.0, 62.7, 33.3, 29.0, 28.9, 28.8, 28.6, 28.5, 25.6; LRESI-MS: *m/z* = 661 $[M+H]^+$; HRESI-MS: *m/z* = 660.42554 $[M+H]^+$ (calc. for $C_{41}H_{58}O_6N$ 660.42586).



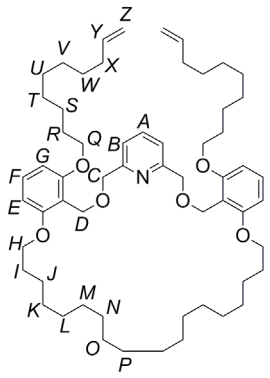
25

Dialkene **24** (1.24 g, 1.88 mmol) in degassed CH_2Cl_2 (50 mL) was added to a solution of Grubbs' 1st generation catalyst ($PhCH=Ru(PCy_3)_2Cl_2$, 155 mg, 0.19 mmol) in degassed CH_2Cl_2 (500 mL) and the reaction allowed to stir at rt for 24 h. A second portion of Grubbs' 1st generation catalyst (155 mg, 0.19 mmol) was added and the reaction mixture allowed to stir for a further 24 h. Ethyl vinyl ether (2 mL) was added and the solution under reduced pressure. Column chromatography of the resulting residue (petrol-EtOAc, 4:1) gave **25** (533 mg, 47%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br-s, 2H, OH), 7.75 (t, 1H, *J* = 7.7, H_A), 7.32 (d, 2H, *J* = 7.7, H_B), 7.13 (td, 2H, *J* = 8.2, 2.3, H_F), 6.56 (d, 2H, *J* = 7.9, H_G or H_E), 6.04 (d, 1.4H, H_G or H_E-*major*), 6.39 (d, 0.6H, *J* = 7.8, H_G or H_E-*minor*), 5.36-5.32 (m, 2H, H_P-mixture of *cis* and *trans*), 4.93 (s, 2.8H, H_C-*major*), 4.91 (s, 1.2H, H_C-*minor*), 4.84 (s, 4H, H_D), 3.94-3.89 (m, 4H, H_H), 2.02-1.97 (m, 1H, H_O-*minor*), 1.96-1.92 (m, 3H, H_O-*major*), 1.74-1.65 (m, 4H, H_I), 1.43-1.24 (m, 20H, H_J, H_K, H_L, H_M, H_N); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 157.2, 157.0, 137.9, 130.3, 129.4, 120.1, 110.7, 109.5, 103.0, 72.1, 68.2, 65.1, 32.3, 29.3, 29.2, 29.0, 29.0, 28.5, 26.1; LRESI-MS: *m/z*: 633 $[M+H]^+$; HRESI-MS: *m/z* = 632.39600 (calc. for $C_{39}H_{54}O_6N$ 632.39456).



26

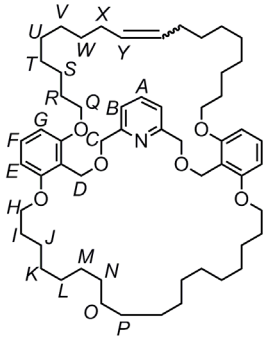
Pd/C (89 mg of a 10% w/w dispersion) was added to a solution of **25** (613 mg, 0.84, 0.97 mmol) in THF (40 mL). The reaction mixture was allowed to stir under an atmosphere of $H_{2\ (g)}$ for 8 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to give macrocycle **26** (611 mg, 99%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (br, 2H, OH), 7.75 (t, 1H, *J* = 7.7, H_A), 7.32 (2H, d, *J* = 7.7, H_B), 7.13 (t, 2H, *J* = 8.2, H_F), 6.56 (d, 2H, *J* = 7.7, H_G), 6.41 (d, 2H, *J*= 8.2, H_E), 4.94 (s, 4H, H_C), 4.84 (s, 4H, H_D), 3.94 (t, 4H, *J* = 5.9, H_H), 3.76-3.73 (m, 4H, H_I), 1.87-1.84 9 (m, 4H, H_J), 1.75-1.68 (m, 4H, H_K), 1.45-1.37 (m, 4H, H_L), 1.32-1.24 (m, 16H, H_M, H_N, H_O, H_P); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 157.2, 157.1, 137.9, 129.4, 120.0, 110.7, 109.5, 103.0, 72.1, 68.2, 65.1, 29.3, 29.2, 29.2, 29.1, 29.0, 29.0, 26.1, 25.5; LRESI-MS: *m/z* = 634 $[M+H]^+$; HRESI-MS: *m/z* = 634.41005 $[M+H]^+$ (calc. for $C_{39}H_{56}O_6N$ 634.41021).



27

NaH (61.4 mg, 2.56 mmol) was added to a solution of diphenol **26** (540 mg, 0.85 mg) in DMF (15 mL) at 0 ºC. After 10 minutes, 10-bromodecene (1.03 mL, 5.11 mmol) was added and the reaction was allowed to warm from 0 ºC to rt then stirred for a further 18 h at rt. A few drops of H_2O were carefully added to quench the reaction

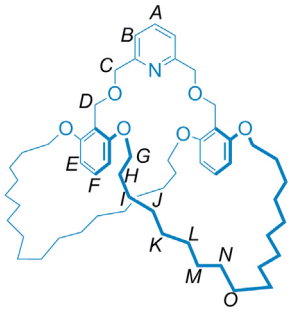
then the reaction mixture was filtered through celite. EtOAc (100 mL) and H_2O (100 mL) were added and the phases separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with H_2O (2 x 100 mL) then brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the resulting residue (petrol-EtOAc, 9:1) gave **27** (433 mg, 56%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, 1H, *J* = 7.9, H_A), 7.47 (d, 2H, *J* = 7.7, H_B), 7.19 (t, 2H, *J* = 8.3, H_F), 6.52 (d, 4H, *J* = 8.4, H_E and H_G), 5.86-5.75 (m, 2H, H_Y), 4.98 (ddt, 2H, J_d = 17.2, 1.8, J_t = 1.5, H_Z-*trans*), 4.92 (*app*-d, 2H, J_d = 10.2, H_Z-*cis*), 4.75 (s, 4H, H_C), 4.73 (s, 4H, H_D), 3.97 (t, 8H, *J* = 6.3, H_H and H_Q), 2.05-1.99 (m, 4H, H_X), 1.83-1.73 (m, 8H, H_I and H_R), 1.50-1.17 (m, 48H, H_J, H_K, H_L, H_M, H_N, H_O, H_P, H_S, H_T, H_U, H_V and H_W); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (Cx2), 158.7, 139.0, 136.5, 129.5, 125.4, 119.2, 114.1, 104.5 (Cx2), 73.3, 68.5, 68.4, 61.5, 34.0, 33.7, 32.7, 29.4, 29.3 (Cx2), 29.1, 29.0, 28.9, 28.8 (2xC), 28.6, 28.1, 26.1, 26.0; LRESI-MS: *m/z* = 911 $[M+H]^+$; HRESI-MS: *m/z* = 910.69197 $[M+H]^+$ (calc. for $C_{59}H_{92}O_6N$ 910.69192).



28

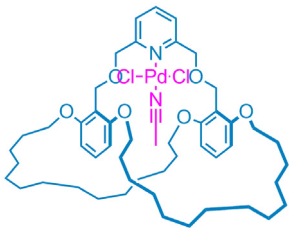
A solution of **27** (433 mg, 475 μmol) in degassed CH_2Cl_2 (50 mL) was added to a solution of Grubbs' 1st generation catalyst ($PhCH=Ru(PCy_3)_2Cl_2$, 391 mg, 47.5 μmol) in degassed CH_2Cl_2 (500 mL). The reaction mixture was allowed to stir under an atmosphere of $N_{2\,(g)}$ for 18 h. Ethyl vinyl ether (1 mL) was added to quench the catalyst and the solution concentrated under reduced pressure. Column chromatography of the resulting residue (petrol-EtOAc, 9:1) gave **28** (350 mg, 83%) as a colorless solid. M.p. 92-95 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, 1H, *J* = 7.7, H_A), 7.48 (d, 2H, H_B), 7.19 (t, 2H, *J* = 8.3, H_F), 6.52 (d, 4H, *J* = 8.4, H_E and

H_G), 5.38-5.34 (m, 2H, H_Y- mixture of *cis* and *trans*), 4.74 (s, 8H, H_C and H_D), 3.97 (td, 8H, J_t = 6.2, J_d = 1.7, H_H and H_Q), 2.02-1.97 (m, 4H, H_X), 1.84-1.77 (m, 8H, H_I and H_R), 1.50-1.44 (m, 8H, H_J and H_S), 1.38-1.29 (m, 40H, H_K, H_L, H_M, H_N, H_O, H_P, H_T, H_U, H_V and H_W); ^{13}C NMR (100 MHz, $CDCl_3$): δ =158.9 (Cx2), 158.7, 136.7, 130.4, 129.6, 119.3, 114.4, 104.4 (Cx2), 73.5, 68.5, 68.5, 61.6, 32.2, 29.4 (3xC), 29.3, 29.2, 29.1 (3xC), 29.0, 28.9 (2xC), 28.8, 28.4, 26.0; LRESI-MS: *m/z* = 883 $[M+H]^+$; HRESI-MS: *m/z* = 882.65983 $[M+H]^+$ (calc. for $C_{57}H_{88}O_6N$ 882.66062).



1b

Pd/C (41 mg of a 10% w/w dispersion) was added to a solution of **28** (340 mg, 385 μmmol) in THF (20 mL) and the reaction mixture allowed to stir for 5 h under an atmosphere of $H_{2\,(g)}$. The reaction mixture was filtered through celite and evaporated under reduced pressure to give macrocycle **1b** (334 mg, 98%) as a colorless solid. M.p. 73-76 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (t, 1H, *J* = 7.7, H_A), 7.48 (d, 2H, *J* = 7.7, H_B), 7.19 (t, 2H, *J* = 8.3, H_F), 6.52 (d, 4H, *J* = 8.4, H_E), 4.76 (s, 4H, H_C), 4.75 (s, 4H, H_D), 3.97 (t, 8H, *J* = 6.4, H_G), 1.84-1.77 (m, 8H, H_H), 1.51-1.44 (m, 8H, H_I), 1.37-1.25 (m, 48H, H_J, H_K, H_L, H_M. H_N, H_O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 158.7, 136.7, 129.6, 119.3, 114.4, 104.4, 73.5, 68.5, 61.7, 29.3, 29.1, 29.1, 29.0, 28.8 (2xC), 28.7, 26.0; LRESI-MS: *m/z* = 885 $[M+H]^+$; HRESI-MS: *m/z* = 884.67693 (calc. for $C_{57}H_{90}NO$ 884.67627).



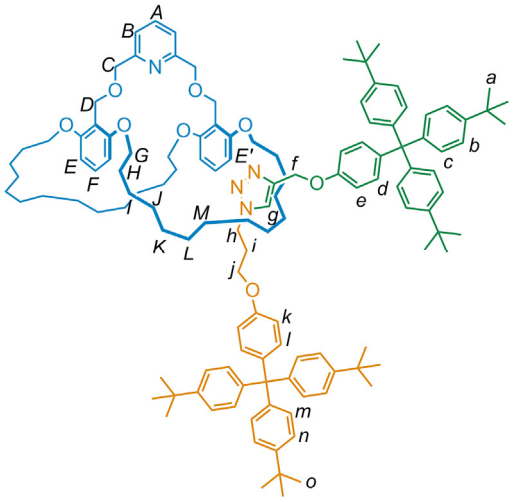
1a.$PdCl_2$(MeCN)

A solution of macrocycle **1a** (50.0 mg, 65 μmol) in CH_2Cl_2 (2.5 mL) was added to a solution of *trans*-$PdCl_2(MeCN)_2$ (16.9 mg, 65 μmol) in MeCN (2.5 mL) and the resulting solution stirred for 1 h at rt. Volatiles were removed under reduced pressure to leave **1a**.$PdCl_2$(MeCN) as a yellow/orange solid. Single crystals, suitable for X-ray diffraction, were grown by slow cooling of a saturated solution of this crude product in MeCN.

3.4.2 Synthesis of Rotaxanes 5, 6b, 9b and 13b

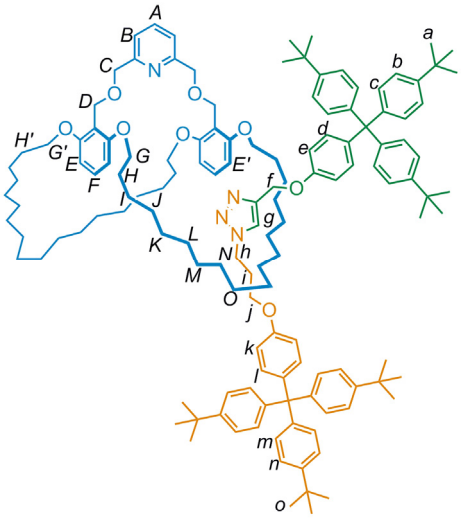
General Procedure for the Synthesis of [2]- and [3]Rotaxanes with Triazole Threads

Alkyne (5.0 equiv.) and azide (5.0 equiv.) were added to a solution of macrocycle (1.0 equiv.) and $[Cu(CH_3CN)_4](PF_6)$ (1.0 equiv.) in $ClCH_2CH_2Cl$. The solution was heated to 70 ºC and allowed to stir at this temperature for 24 h. To increase the yield of [3]rotaxane over [2]rotaxane, a further 5.0 equiv. of alkyne and 5.0 equiv. of azide were added after 24 h and the reaction mixture stirred for an additional 24 h at 70 ºC. The reaction mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (100 mL). This organic phase was washed with a 17.5% solution of NH_3 saturated with EDTA (3 x 100 mL), water (100 mL) then brine (100 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography gave the [2]- and/or [3]rotaxane.



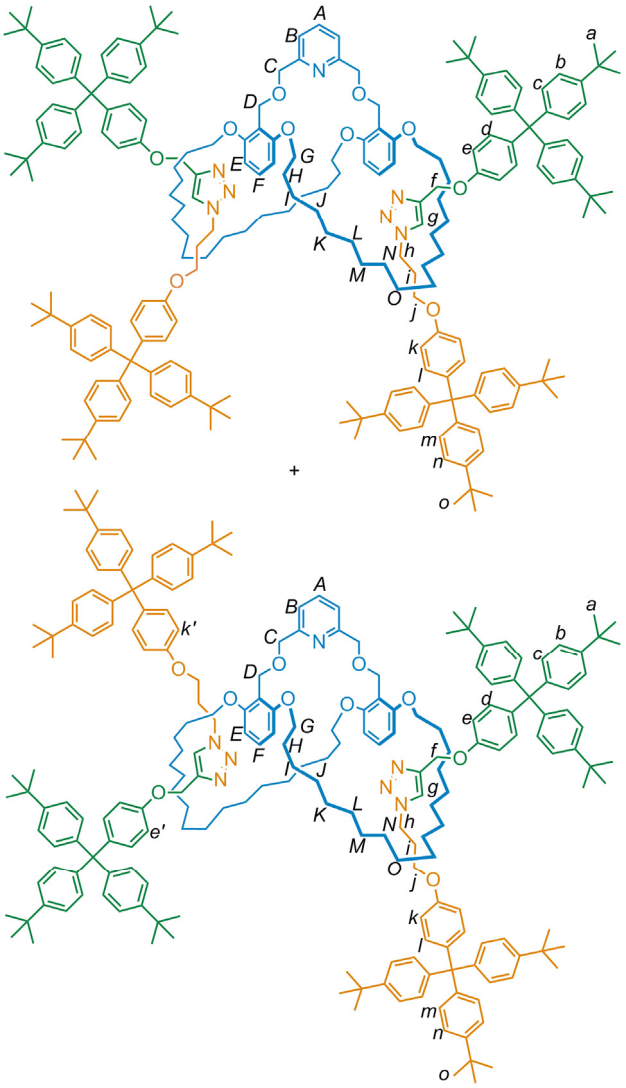
5a

Following the general procedure, alkyne **2** (51.5 mg, 95 µmol), azide **3** (56.0 mg, 95 µmol) and macrocycle **1a** (15.0 mg, 19 µmol) were reacted in $ClCH_2CH_2Cl$ (2 mL). Column chromatography (gradient elution: petrol-Et_2O, 1. 20:1, 2. 10:1, 3. 5:1, 4. 4:1, 5. 3:1) gave [2]rotaxane **5a** (15 mg, 41%) as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1H, H_g), 7.33 (t, 1H, *J* = 7.7, H_A), 7.23 (d, 6H, *J* = 8.7, H_b or H_n), 7.21 (d, 6H, *J* = 8.7, H_b or H_n), 7.17 (d, 2H, *J* = 7.7, H_B), 7.10 (d, 12H, *J* = 8.4, H_c and H_m), 7.06-7.02 (m, 6H, H_d, H_l and H_F), 6.77 (d, 2H, *J* = 8.9, H_e), 6.69 (d, 2H, *J* = 8.9, H_k), 6.44 (d, 2H, *J* = 8.3, H_E or H_E'), 6.36 (d, 2H, *J* = 8.4, H_E or $H_{E'}$), 4.85 (s, 2H, H_f), 4.70 (s, 4H, H_C), 4.56 (s, 4H, H_D), 4.18 (t, 2H, *J* = 7.9, H_h), 3.93 (t, 4H, *J* = 5.5, H_G or $H_{G'}$), 3.78 (t, 2H, *J* = 5.5, H_j), 3.71 (t, 4H, J_t = 7.4, H_G or $H_{G'}$), 2.10-2.03 (m, 2H, H_i), 1.78-1.71 (m, 4H, H_H or $H_{H'}$), 1.63-1.56 (m, 4H, H_H or $H_{H'}$), 1.54-1.46 (m, 4H, aliphatic CH_2), 1.29 (m, 54H, H_a and H_o), 1.27-1.26 (m, 18H, aliphatic CH_2), 1.16-1.06 (m, 18H, aliphatic CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 158.6, 157.8, 156.4, 156.4, 148.1 (Cx2), 144.2 (Cx2), 143.3, 139.4, 139.3, 136.4, 132.0, 132.0, 130.7 (Cx3), 129.6, 123.9 (Cx2), 120.5, 114.2, 113.1, 113.0, 104.3, 104.0, 73.8, 68.9, 68.0, 64.3, 63.0, 61.7, 61.6 (2xC), 47.0, 34.2 (Cx2), 29.7, 29.6 (Cx3), 29.5, 29.4, 29.3, 29.1 (Cx2) 28.7, 26.4, 25.8; LRESI-MS 1904 $[M+H]^+$ HRFAB-MS (3-NOBA matrix): *m/z* = 1903.30073 $[M+H]^+$ (calc. for $C_{128}H_{169}{}^{13}CN_4O_8$ 1903.29740).



5b

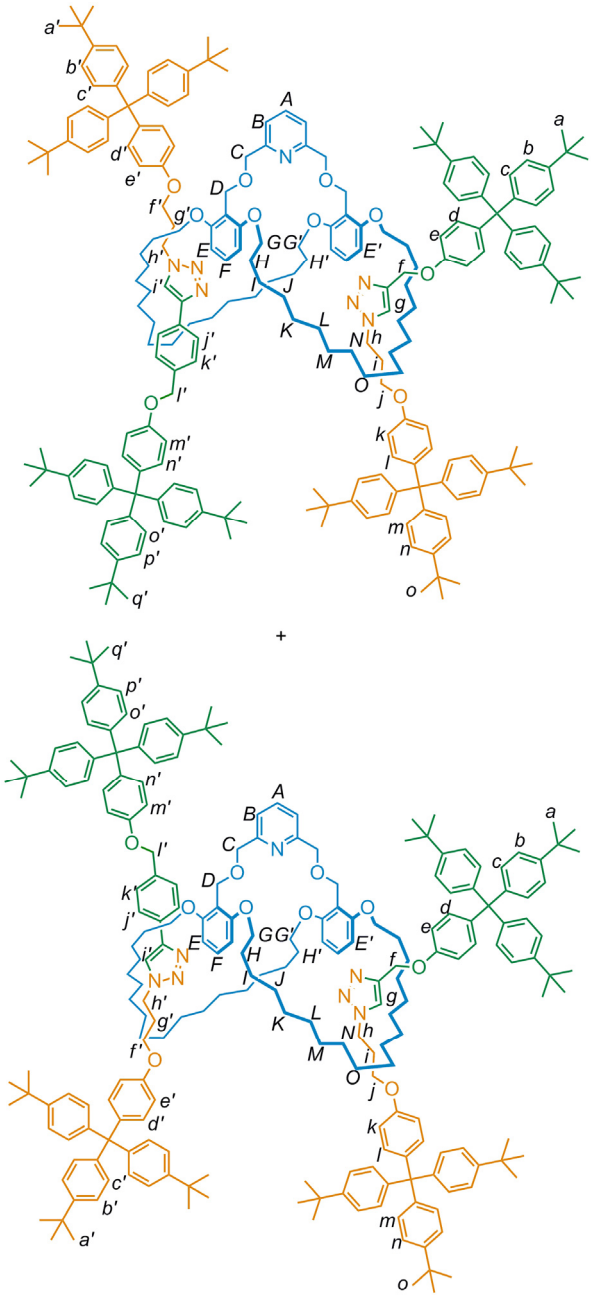
Following the general procedure, alkyne **2** (307 mg, 565 µmol), azide **3** (332 mg, 565 µmol) and macrocycle **1b** (100 mg, 113 µmol) were reacted in $ClCH_2CH_2Cl$ (4 mL). Column chromatography (gradient elution: 1. $CHCl_3$, 2. $CHCl_3$ with 0.5→3% acetone) gave [2]rotaxane **5b** (131 mg, 57%) as a colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (s, 1H, H_g), 7.32 (t, 1H, *J* = 7.6, H_A), 7.23-7.20 (d, 6H, *J* = 7.2, H_b or H_n), 7.20-7.18 (d, 6H, *J* = 7.2, H_b or H_n), 7.17 (d, 2H, *J* = 7.7, H_B), 7.08 (d, 16H, *J* = 8.6, H_c, H_d, H_l, H_m), 7.05 (t, 2H, *J* = 8.8, H_F), 6.78 (d, 2H, *J* = 8.9, H_e), 6.68 (d, 2H, *J* = 8.9, H_k), 6.45 (d, 2H, *J* = 8.4, H_E or $H_{E'}$), 6.37 (d, 2H, *J* = 8.3, H_E or H_E'), 4.95 (s, 2H, H_f), 4.69 (s, 4H, H_C), 4.58 (s, 4H, H_D), 4.24 (t, 2H, *J* = 7.6, H_h), 3.90 (t, 4H, *J* = 6.3, H_G or $H_{G'}$), 3.79-3.73 (m, 6H, H_j and H_G or $H_{G'}$), 2.12-2.05 (m, 2H, H_i), 1.76-1.72 (m, 4H, H_H or $H_{H'}$), 1.61-1.56 (m, 4H, H_H or $H_{H'}$), 1.48-1.41 (m, 8H, H_I), 1.29 (s, 27H, H_a or H_o), 1.28 (s, 27H, H_a or H_o), 1.25-1.24 (m, 48H, H_J, H_K, H_L, H_M, H_N, H_O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 158.7, 158.2, 156.3, 148.1 (Cx2), 144.1 (Cx2), 139.6 (Cx2), 136.6, 132.1, 132.0, 130.6, 130.6, 129.6, 124.0 (Cx2), 119.9, 114.2 (Cx2), 113.1, 113.0, 104.4, 104.2, 73.5, 68.7, 68.4, 64.1 (Cx2), 61.7, 53.0, 47.1, 44.4, 34.2 (Cx2), 31.3 (Cx2), 29.6, 29.4, 29.3, 29.2, 29.2, 29.0, 28.9, 28.9, 28.9, 28.8, 26.0, 25.7; LRESI-MS: *m/z* = 2015 $[M]^+$ and 2016 $[M+H]^+$; HRESI-MS: *m/z* = 2015.43037 $[M+H]^+$ (calc. for $C_{137}H_{185}N_4O_8$ 2015.42707).



syn-**6b** + *anti*-**6b**

Following the general procedure, alkyne **2** (307 mg, 565 µmol), azide **3** (332 mg, 565 µmol) and macrocycle **1b** (100 mg, 113 µmol) were reacted in $ClCH_2CH_2Cl$ (4 mL). After 24 h a further portion of alkyne **2** (307 mg, 565 µmol) and azide **3** (332 mg, 565 µmol) were added and the reaction mixture was allowed to stir for a further 24 h. Column chromatography (gradient elution: 1. $CHCl_3$, 2. $CHCl_3$ with 0.5→3% acetone) gave [3]rotaxane **6b**, as a mixture of isomers *syn*-**6b** and *anti*-**6b**, (31.4 mg, 86%) as a colorless solid. M.p. 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 2H, H_g), 7.21-7.18 (m, 24H, H_b and H_n), 7.07 (d, 24H, J_d = 8.6, H_c and H_m), 7.04-6.97 (m, 11H, H_d, H_l, H_F and H_A), 6.86 (d, 2H, J = 7.8, H_B), 6.72 (d, 2H, J = 8.9, *syn* or *anti* H_e), 6.71 (d, 2H, J = 8.9, *syn* or *anti* H_e), 6.60 (d, 2H, J = 8.9, *syn* or

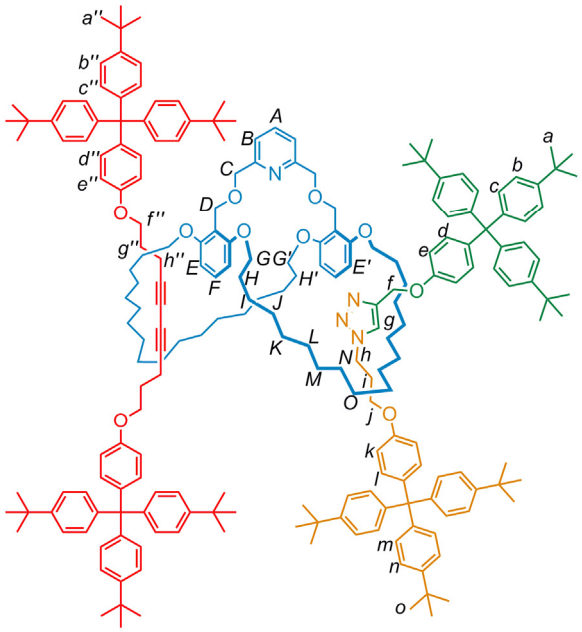
anti H_k), 6.59 (d, 2H, *J* = 8.9, *syn* or *anti* H_k), 6.32 (d, 4H, *J* = 8.4, H_E), 4.86 (s, 4H, H_f), 4.67 (s, 4H, H_C), 4.44 (s, 4H, H_D), 4.17 (t, 4H, *J* = 7.2, H_h), 3.72 (t, 8H, *J* = 6.9, H_G), 3.68 (t, 4H, *J* = 5.9, H_j), 2.04-1.98 (m, 4H, H_i), 1.61-1.52 (m, 8H, H_H), 1.27 (d, 108H, *J*= 2.4, H_a and H_o), 1.06-1.02 (m, 56H, H_I, H_J, H_K, H_L, H_M, H_N, H_O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 157.7, 156.2, 148.1 (2xC), 144.1 (2xC), 143.5, 139.6, 139.5, 136.5, 132.0, 132.0, 130.6, 130.6, 129.7 (2xC), 124.0 (2xC), 123.3, 120.2, 114.1, 113.0, 112.9, 104.3, 73.4, 68.6 (2xC), 65.8, 64.0, 63.0, 61.8, 61.6, 47.1, 41.3 (2xC), 34.2 (2xC), 31.3, 29.8, 29.6, 29.4, 29.4, 29.3, 29.1, 29.0, 25.8, 20.4; LRESI-MS: *m/z* = 3146 $[^{13}C_2M]^+$ and 3147 $[^{13}C_2M+H]^+$; HRESI-MS: *m/z* = 3146.16929 $[^{13}C_2M+H]^+$ (calc. for $C_{215}{}^{13}C_2H_{280}N_7O_{10}$ 3146.17285).



syn-**9b** + *anti*-**9b**

Alkyne **7** (58.5 mg, 94 μmol) and azide **3** (55.6 mg, 94 μmol) were added to a solution of [2]rotaxane **5b** (38 mg, 19 μmol) and $[Cu(CH_3CN)_4]PF_6$ (7 mg, 19 μmol) in $ClCH_2CH_2Cl$ (not anhydrous). The solution was heated to 70 ºC and allowed to stir at this temperature for 18 h. The reaction mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (30 mL). This organic phase was washed with a 17.5% solution of NH_3 saturated with EDTA (3 x 30 mL), water (30 mL) then brine

(30 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (1. $CHCl_3$, 2. $CHCl_3$ with 0.5→2% acetone) followed by preparative TLC on silica gel ($CHCl_3$ with 1% acetone) gave [3]rotaxane **9b,** as a mixture of isomers *syn*-**9b** and *anti*-**9b,** (26 mg, 43%) as a colorless solid. M.p. 130-132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (d, 2H, *J* = 4.1, $H_{g'}$), 7.66-7.62 (m, 2H, H_g and $H_{i'}$), 7.53-7.52 (m, 2H, $H_{h'}$), 7.22-7.14 (m, 27H, H_A, H_B, H_b, $H_{b'}$, H_n and $H_{p'}$), 7.09-6.93 (m, 34H, H_c, $H_{c'}$, H_d, $H_{d'}$, H_l, H_m, $H_{n'}$ and $H_{o'}$), 6.77-6.69 (m, 4H, H_e and $H_{e'}$), 6.67-6.57 (m, 4H, H_k and $H_{m'}$), 6.36-6.32 (m, 4H, H_E and $H_{E'}$), 4.86 (s, 4H, H_f and $H_{f'}$), 4.69 (s, 4H, H_C), 4.44 (s, 4H, H_D), 4.23 (t, 2H, *J* = 7.1, $H_{j'}$), 4.16 (t, 2H, *J* = 7.0, H_h), 3.77-3.65 (m, 12H, H_f, H_G, $H_{G'}$ and H_j), 2.15-1.99 (m, 4H, $H_{k'}$ and H_l), 1.66-1.52 (m, 8H, H_H), 1.28-0.80 (m, 164H, H_a, $H_{a'}$, H_o, $H_{q'}$ and H_{alkyl}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.8, 157.7, 156.6, 156.2, 156.2, 148.1, 146.9, 144.5, 144.2, 144.1, 139.6, 137.7, 137.0, 136.5, 132.1, 132.0, 130.7, 129.7, 127.7, 125.6, 125.5, 124.0, 123.8, 123.6, 123.3, 120.5, 120.3, 114.1, 113.2, 113.1, 112.9, 104.3, 104.3, 73.5, 69.5, 68.7, 64.1, 64.1, 63.0, 61.8, 61.6, 47.1, 34.2, 31.3, 29.8, 29.7, 29.4, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 25.8; LRESI-MS: *m/z* = 3222 $[^{13}C_2M+H]^+$; HRFAB-MS: *m/z* = 3222.20564 $[^{13}C_2M+H]^+$ (calc. for $C_{221}{}^{13}C_2H_{284}N_7O_{10}$ 3222.19968).



13b

Under an inert N_2 atmosphere diisopropylamine (57.0 mg, 560 µmol), copper iodide (21.5 mg, 110 µmol), macrocycle **1b** (47.5 mg, 54 µmol) and iodine (7.2 mg, 28 µmol) were added sequentially to a solution of alkyne **10** (971 mg, 1.7 mmol) in anhydrous benzene (2 mL) at rt. A solution of the corresponding palladium-macrocycle complex was added slowly over a period of 12 h with a syringe pump, this was prepared by adding a solution of macrocycle **1b** (2.5 mg, 3 µmol) in CH_2Cl_2 (0.5 mL) to a solution of bis(acetonitrile)dichloropalladium(II) (730 µg, 3 µmol) in CH_3CN (0.5 mL), stirring for 1 h at rt before concentrating under reduced pressure then dissolving the resulting residue in anhydrous benzene (1 mL). When the addition was complete the reaction mixture was allowed to stir for a further 120 h after which time the crude product was taken into a partition of CH_2Cl_2 (15 mL) and a saturated aqueous solution of sodium ethylenediaminetetraacetate (Na_4EDTA, 15 mL) and stirred for 1 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue, containing [2]rotaxane **12b**, was partially purified on a short plug of silica gel flushing with $CHCl_3$ to remove the major by-products then eluting the remaining mixture with 10% acetone in $CHCl_3$. The resulting [2]rotaxane **12b** containing mixture was dissolved in $ClCH_2CH_2Cl$ (4

mL), $[Cu(CH_3CN)_4](PF_6)$ (21 mg, 57 μmol), alkyne **2** (308 mg, 570 μmol) and azide **3** (332 mg, 570 μmol) were added and the resulting mixture was heated to 70 ºC and stirred for 18 h. The reaction mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (100 mL). This organic phase was washed with a 17.5% solution of NH_3 saturated with EDTA (3 x 100 mL), H_2O (100 mL) then brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC on silica gel ($CHCl_3$ with 1% acetone) gave [3]rotaxane **13b** (7 mg, 4%) as a film. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (s, 1H, H_g), 7.21-7.18 (m, 27H, H_A, H_B, H_b, $H_{b''}$ and H_n), 7.08-6.98 (m, 32H, H_c, $H_{c''}$, H_d, H_F, H_k, H_l and H_m), 6.75 (dd, 2H, J = 2.8, J = 9.6, H_e), 6.64-6.59 (m, 10H, $H_{d''}$, $H_{e''}$ and H_k), 6.36-6.33 (m, 4H, H_E and $H_{E'}$), 4.91 (s, 2H, H_f), 4.69 (s, 4H, H_C), 4.53 (s, 4H, H_D), 4.25-4.19 (m, 2H, H_h), 3.79-3.65 (m, 14H, $H_{f''}$, H_G, $H_{G'}$ and H_j), 2.27 (t, 4H, J = 7.0, $H_{h''}$), 2.07-1.99 (m, 2H, H_i), 1.77-1.65 (m, 12H, $H_{g''}$, H_H and $H_{H'}$), 1.33-1.13 (m, 164H, H_a and H_{alkyl}); ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 158.9, 158.8, 158.1, 156.4, 148.1, 144.2, 139.3, 132.1, 132.0, 130.7, 126.8, 124.0, 119.8, 117.1, 114.4, 113.1, 113.0, 112.9, 104.4, 104.3, 73.5, 68.7, 68.7, 65.7, 61.7, 56.9, 53.4, 50.9, 34.2, 32.1, 31.9, 31.7, 31.3, 30.0, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 29.2, 29.0, 28.2, 27.0, 26.3, 26.0, 25.8, 24.8, 22.6, 16.0, 14.1; LRESI-MS: *m/z* = 3156 $[^{13}C_2M+H]^+$; HRFAB-MS: *m/z* = 3155.18175 $[^{13}C_2M+H]^+$ (calc. for $C_{219}{}^{13}C_2H_{283}N_4O_{10}$ 3155.18264).

3.4.3 Crystal Data and Structure Refinement for 1a.PdCl$_2$(MeCN)

Empirical formula	$C_{51}H_{76}Cl_2N_2O_6Pd$
Formula weight	990.44
Temperature	93(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 18.431(5) Å α= 90°.

	b = 21.805(6) Å β= 102.806(4)°.
	c = 12.751(4) Å γ = 90°.
Volume	4997(3) $Å^3$
Z	4
Density (calculated)	1.316 Mg/m^3
Absorption coefficient	0.527 mm^{-1}
F(000)	2096
Crystal size	0.2000 x 0.1000 x 0.0800 mm^3
Theta range for data collection	1.13 to 25.40°.
Index ranges	$-21 \leq h \leq 22$, $-24 \leq k \leq 26$, $-15 \leq l \leq 15$
Reflections collected	47896
Independent reflections	9169 [R(int) = 0.0490]
Completeness to theta = 25.00°	99.8 %
Absorption correction	Multiscan
Max. and min. transmission	1.0000 and 0.9288
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9169 / 40 / 562
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0855, wR2 = 0.2288
R indices (all data)	R1 = 0.0928, wR2 = 0.2379

Extinction coefficient	0.0020(7)
Largest diff. peak and hole	1.716 and -1.139 e.Å^{-3}

3.5 References

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CHAPT. 4 | ACTIVE METAL TEMPLATE SYNTHESIS OF [2]CATENANES

Published as *'Active Metal Template Synthesis of [2]Catenanes'*– Goldup, S. M.; Leigh, D. A.; Long, T.; McGonigal, P. R.; Symes, M. D.; Wu, J. *J. Am. Chem. Soc.* **2009**, *131*, 15924–15929.

Synopsis

This Chapter describes the synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu^{I} ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure. Appropriately functionalized pyridine ether or bipyridine ligands are employed in either a CuAAC "click" AMT reaction or a Cu^{I}-mediated Cadiot-Chodkiewicz AMT heterocoupling of an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit [2]catenanes (where the rings are constitutionally different) are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit [2]catenane (two identical rings) in 46% yield through a one-pot, double macrocyclization, procedure. Remarkably, less than 7% of the corresponding noninterlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu^{I} as both a template for the catenane and a catalyst for covalent bond formation in the reaction.

Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Jhenyi Wu carried out all investigations into the Cadiot-Chodkiewicz AMT synthesis of catenane **3** and, together with the Author and Dr. Mark Symes, studied the single macrocyclization CuAAC AMT reactions. Tao Long synthesized a variety of building blocks. Dr. Symes and Dr. Stephen Goldup made crucial contributions to the project design and writing process.

4.1. Introduction

The synthesis of catenanes and rotaxanes was revolutionized by the application of template-directed syntheses,[1] in which the components are preorganized prior to covalent capture of the interlocked architecture. Although a large number of different types of template-directed reactions have been successfully employed to form rotaxanes in threading-followed-by-stoppering strategies,[1a] "clipping" approaches to rotaxanes and catenanes (involving single or double macrocyclization of ligands, directed by the template)[2] are rather more demanding and have only been demonstrated with a small number of different macrocyclization reaction types. Of these, Williamson ether synthesis,[2] the Huisgen-Meldal-Fokin Cu^{I}-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC "click" reaction),[3,4] amide or ester bond-forming reactions,[5] ring-closing metathesis,[6] imine bond formation,[1u,6f,7] and metal-ligand coordination[8] are the most commonly used. The effectiveness of these reactions for catenane synthesis lies in their reactive end groups being sufficiently stable in solution to react overwhelmingly in the desired fashion even when accessing the required reaction geometry is a rare event (as it is for the cyclization of large rings), and hence give predominantly macrocyclic products under high dilution. The yield of catenane versus noninterlocked macrocycle then depends on how effectively the template preorganizes the ring-closing reaction to take place while one component is threaded through the cavity of the other.

We recently developed[9] an approach to rotaxane synthesis in which a metal ion ligated endotopically within a macrocycle mediates bond formation between two suitably functionalized building blocks through the macrocycle cavity to assemble the thread. This "active metal template" strategy[9] takes inspiration from ligand couplings employed in transition metal catalysis and opens up a broad range of metal-mediated bond formations for possible use in the synthesis of rotaxanes, the requirement being that the key bond-forming reaction can be directed by the catalyst to proceed through the macrocyclic cavity rather than external to it. Such active metal template processes, where a single species acts as both the template and the catalyst for

covalent bond formation, clearly also offer potential for the synthesis of catenanes (Figure 4.1).

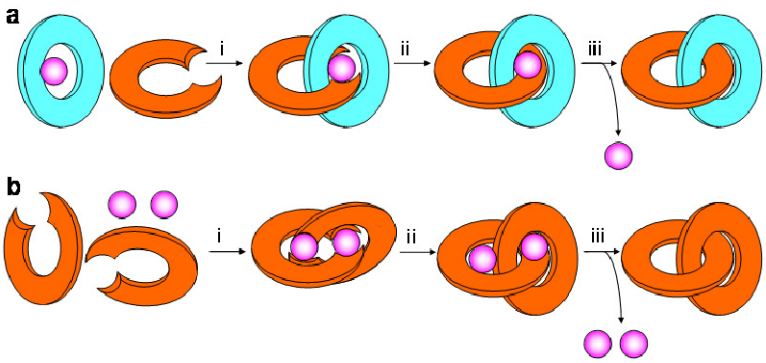


Figure 4.1. The active metal template approach to catenane synthesis. (a) Single macrocyclization route: (i) Template assembly of a macrocyclic ligand and an acyclic ligand about the metal ion (shown in pink) is followed (ii) by a covalent bond-forming reaction between the end groups of the acyclic ligand, catalyzed by the metal ion, through the cavity of the macrocycle. (iii) Decomplexation affords the metal-free [2]catenane. (b) Double macrocyclization route: (i) Template assembly of the acyclic ligands about one or more metal ions is followed by (ii) successive or simultaneous macrocyclization reactions. (iii) Decomplexation affords the metal-free homocircuit (both macrocycles are the same) [2]catenane. The two routes are analogous to the single and double macrocyclization strategies introduced by Sauvage for the synthesis of catenanes by "passive" metal template methods.[2]

Using a metal ion to simultaneously bind to and activate the tethered ends of an acyclic building block to react through the cavity of a macrocycle could lead to reactions with unstable intermediates that would otherwise not lead to interlocked products being used for possible catenane-forming reactions. Active template processes also offer the possibility of traceless assembly[9i] (as the coordinating functional groups are often chemically changed during the reaction into noncoordinating elements) and could be used to prepare catenanes containing multiple rings or having only very weak residual intercomponent interactions, molecules that are often difficult or impossible to achieve with standard template-directed approaches. Here, we report on the application of the active metal template concept to catenane synthesis using both single macrocyclization and double macrocyclization strategies. Heterocircuit (the rings are different) and homocircuit (the rings are the same) [2]catenanes are assembled using appropriately functionalized bidentate pyridine ether or bipyridine ligands and either the Cu^{I}-

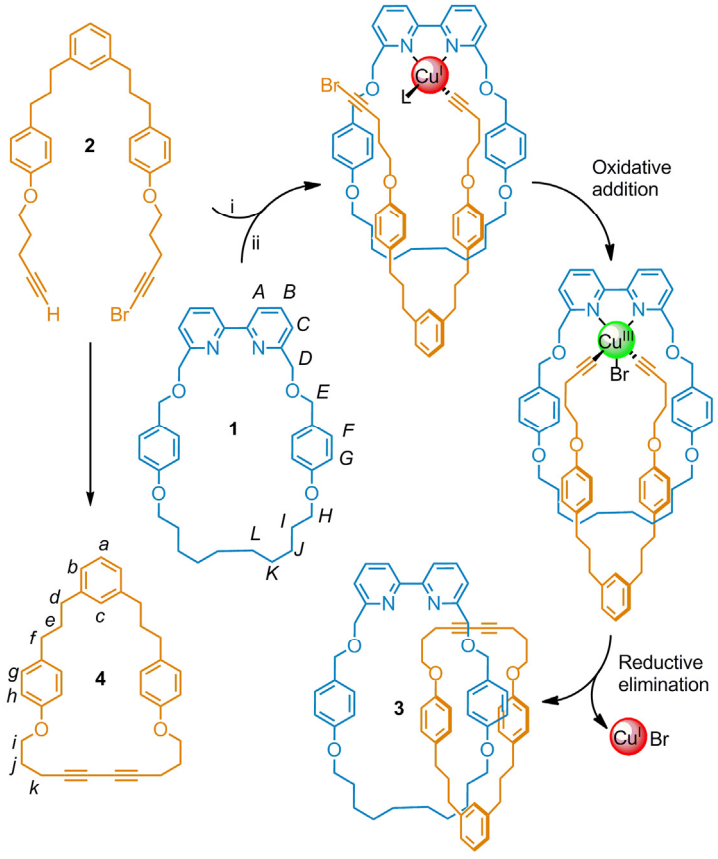
catalyzed CuAAC reaction or the Cu^{I}-mediated Cadiot-Chodkiewicz[10] heterocoupling of an alkynyl halide and a terminal alkyne.

4.2 Results and Discussion

4.2.1 Active Metal Template [2]Catenane Synthesis Using the Cadiot-Chodkiewicz Reaction

We initially investigated a modified Cadiot-Chodkiewicz coupling[11] of a bromoalkyne with a terminal alkyne mediated by a Cu^{I} complex of bidentate bipyridyl macrocycle **1**,[9d] due to its efficacy in active template rotaxane-forming reactions.[9g]

Scheme 4.1. Active Metal Template Cadiot-Chodkiewicz Synthesis of [2]Catenane **3** from Bipyridyl Macrocycle **1** and Alkyne-Bromoalkyne **2**[a]



[a]Reagents and conditions: (i) LiHMDS, THF, -78 °C; (ii) CuI (1 equiv), 5 equiv of **2**, 80 °C, 72 h, 21% (over two steps). L = I, Br, or THF.

Acyclic unit **2** has no potential metal-coordinating sites other than the terminal alkyne and bromoalkyne reactive functional groups and should cyclize to form a ring of similar size and shape to others previously demonstrated to accommodate thread-forming reactions in active template rotaxane syntheses.[9] Building block **2** was treated with LiHMDS ($LiN(SiMe_3)_2$) at -78 °C and then added to a solution of macrocycle **1** and CuI in THF. The resulting mixture was then stirred for 4 days at room temperature (Scheme 4.1), this procedure is similar to that used successfully for rotaxane formation.[9g] Unfortunately, little of the desired catenane product (**3**) was observed, and only a small amount of **2** was consumed under these conditions. Increasing the reaction concentration, raising the reaction temperature to 80 °C, and employing a 5-fold excess of **2** ultimately led to near quantitative conversion and gave [2]catenane **3** in 21% yield. The proposed mechanism for the active metal template Cadiot-Chodkiewicz catenane synthesis is shown in Scheme 4.1.[12] The modest yield illustrates how the catenane-forming reaction, in which the reactive end groups must be tethered together, is much more demanding in terms of conformational requirements of the ligands, and probably steric effects, than the equivalent rotaxane-forming reaction (for which nontethered functional groups are reacted through the macrocycle cavity to form the interlocked thread). The yield of catenane also suffers because the bromoalkyne moiety is present during treatment of the terminal alkyne of **2** with LiHMDS, prior to transmetallation with copper. This leads to some decomposition of the alkyne halide, whereas in the corresponding rotaxane-forming reactions, the terminal alkyne could be treated with LiHMDS and transmetallated with copper before the alkyne halide was added to the reaction mixture.

As a heterocircuit catenane in which the two rings are different, the interlocked nature of **3** was apparent from both mass spectrometry (*m*/*z* of the molecular ion) and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of [2]catenane **3** in $CDCl_3$ (Figure 4.2b) displays upfield shifts of nearly all of the signals with respect to those of the noninterlocked components (Figure 4.2a and c). Such shielding is typical of interlocked architectures in which the aromatic rings of one component are face-on to

another component and is most conspicuous for H_F, H_G, and H_H of macrocycle **1** and H_c, H_h, and H_i of macrocycle **4**. The ubiquity of the upfield shifts implies that the two rings are largely free to rotate with respect to one another, as might be expected in a system where there are no strong intercomponent interactions to stabilize a particular coconformation.

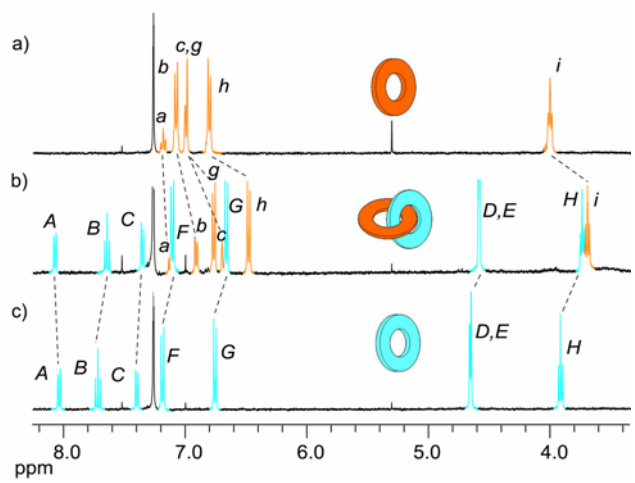


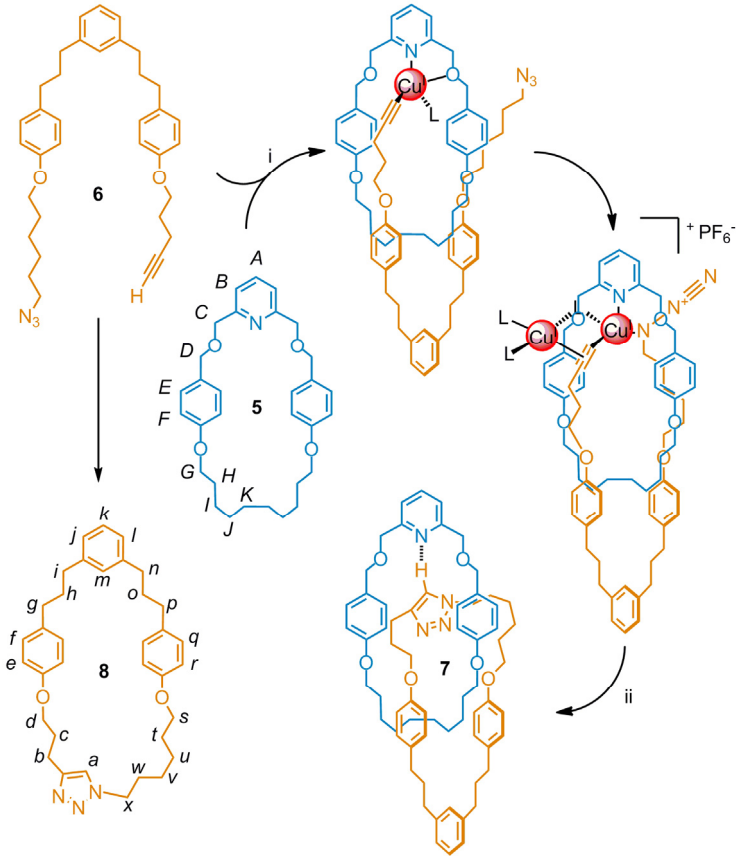
Figure 4.2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) bisacetylene macrocycle **4**, b) [2]catenane **3**, and c) bipyridine macrocycle **1**. The assignments correspond to the lettering shown in Scheme 4.1.

4.2.2 Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Single Macrocyclization Strategy

The qualified success of the catenane-forming active template Cadiot-Chodkiewicz reaction prompted us to try using the CuAAC "click" reaction to form [2]catenanes (Scheme 4.2, Table 4.1), a reaction that had also been previously successfully applied to the active template synthesis of rotaxanes[9a,d] and passive template syntheses of both rotaxanes[1t,13] and catenanes.[4] When an equimolar mixture of macrocycle **5**,[14] $[Cu(CH_3CN)_4](PF_6)$, and the acyclic azide-alkyne unit **6** in dichloromethane was stirred for 24 h at room temperature, a low conversion to triazole products was observed with only trace amounts of catenane apparent in the ^{1}H NMR analysis of the crude reaction mixture (Table 4.1, entry 1). Changing the solvent to 1,2-dichloroethane and raising the temperature to 80 °C afforded [2]catenane **7** in 16% yield with near complete conversion of **6** to triazole products (Table 4.1, entry 2).

Finally, by increasing the number of equivalents of **6** relative to **5** and running the reaction at greater dilution (which required extended reaction times), the yield of catenane **7** was increased to a pleasing 53% (Table 4.1, entry 4). Isolation of the metal-free catenane was facilitated by washing the crude product mixture with a basic EDTA solution.

Scheme 4.2. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **7** from Pyridyl Macrocycle **5** and Azide-Alkyne **6**[a]



[a]Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, CH_2Cl_2, or $C_2H_4Cl_2$; (ii) EDTA, NH_3(aq). L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of conditions and reagent stoichiometry on the reaction yield, see Table 4.1.

Table 4.1. Influence of Reaction Conditions and Reagent Stoichiometry on the Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenanes **7** and **9** (Schemes 2 and 3).[a]

Entry	Macrocycle (concentration)	Equiv. 6	*T* / °C	Time / h	Conversion to triazole products (%)	Yield (%) of [2]catenane 5→7 1→9
1[a]	**5** (6.5 mM)	1	rt	24	15[b]	<5[b]
2	**5** (6.5 mM)	1	80	96	90	16
3	**5** (6.5 mM)	5	80	240	>98	25
4	**5** (1.25 mM)	5	80	288	>98	53
5	**1** (1 mM)	5	80	500	50	50
6	**1** (5 mM)	5	80	170	>98	49

[a]One equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to the macrocycle (**1** or **5**). All reactions were carried out in $C_2H_4Cl_2$, except entry 1 (CH_2Cl_2). [b] Yield estimated by ^{1}H NMR.

The ^{1}H NMR spectrum of catenane **7** (Figure 4.3b) shows significant upfield shifts of various signals (H_x ~0.6 ppm, H_m ~0.4 ppm, H_E ~0.3 ppm, and H_F ~0.3 ppm) with respect to the components (Figure 4.3a and c), consistent with its interlocked architecture. Interestingly, signals corresponding to H_C appear as an A_B system, indicating that the two faces of the pyridyl macrocycle are not equivalent. This is a result of the triazole group making the ring threaded through the pyridyl macrocycle inherently unsymmetrical. The chemical shift of H_a of the triazole group suggests it may form a C-H· · ·N hydrogen bond[15] with the pyridine nitrogen atom of the other macrocycle.

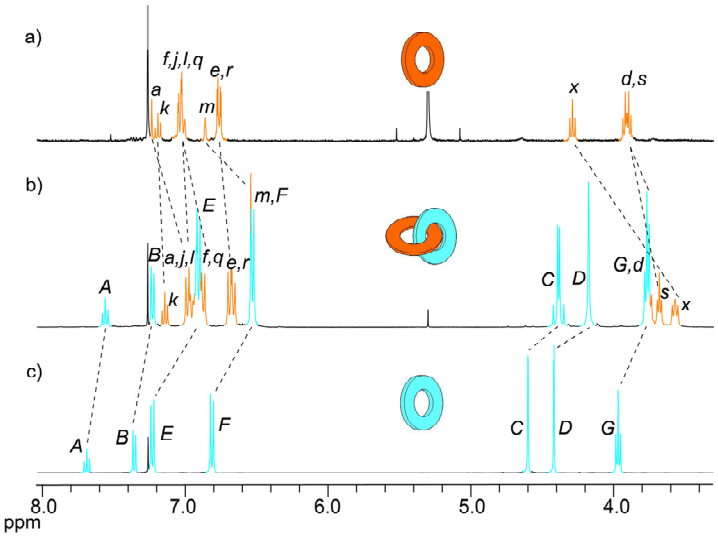
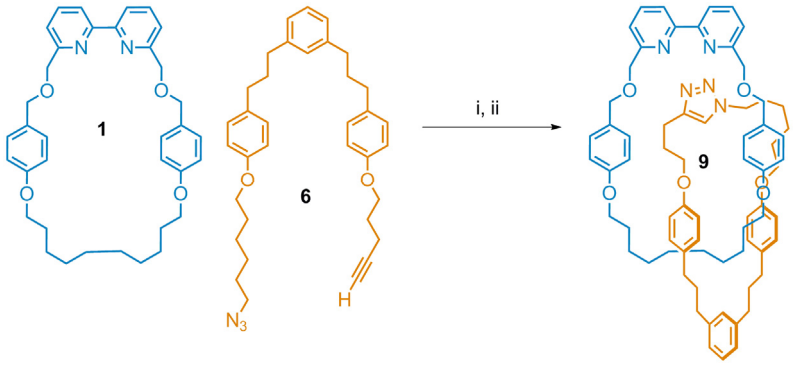


Figure 4.3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) triazole macrocycle **8**, b) [2]catenane **7**, c) pyridine macrocycle **5**. The assignments correspond to the lettering shown in Scheme 4.2.

Both pyridyl and bipyridyl macrocycles have been found to undergo efficient active template rotaxane assembly with the CuAAC reaction,[9d] although the kinetics of the reactions are very different (the bipyridyl macrocycle reaction is considerably slower) as a result of the reactions proceeding through different types of intermediates.[16] The same trend was seen with the active template catenane-forming reaction (Scheme 4.3 and Table 4.1, entries 5 and 6). Although good yields (49-50%) of [2]catenane **9** could be obtained, they required long reaction times (7-21 days) at 80 °C and/or higher reaction concentrations. It is testimony to the very specific reaction preferences of the azide and alkyne functional groups under Cu^{I} catalysis that they survive for so long without undergoing side reactions until the apparently very rare event of the groups being in just the right position to react to form catenane occurs.

Scheme 4.3. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **9** from Bipyridyl Macrocycle **1** and Azide-Alkyne **6**[a]



[a]Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 7-21 d. (ii) EDTA, NH_3(aq), 49-50% (over two steps). For the effect of concentration on the time of reaction, see Table 4.1.

The ^{1}H NMR spectrum of catenane **9** (Figure 4.4b) again shows upfield shifts of most of its signals with respect to its noninterlocked components (Figure 4.4a and c). Signals H_F and H_G of bipyridine macrocycle **1** are each shifted by ~0.2 ppm, consistent with π-π stacking between the aromatic rings to which H_F and H_G are attached and the aromatic rings of macrocycle **8**. As in catenane **7**, the signals corresponding to H_E appear as an AB system, although this is less pronounced than in the pyridine macrocycle-derived catenane.

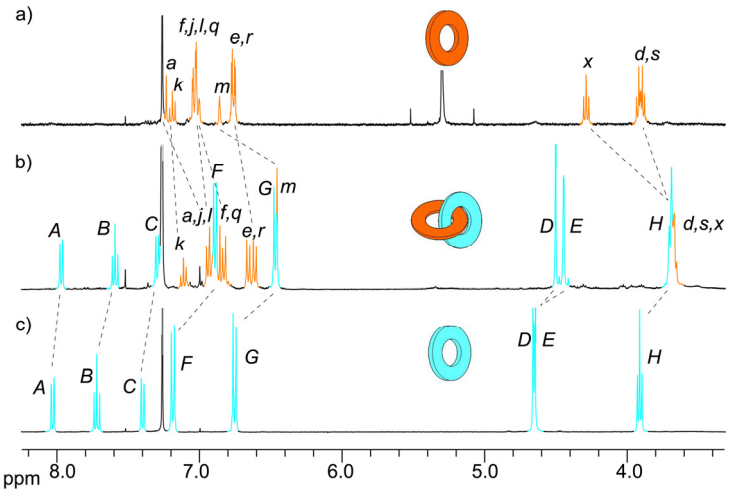


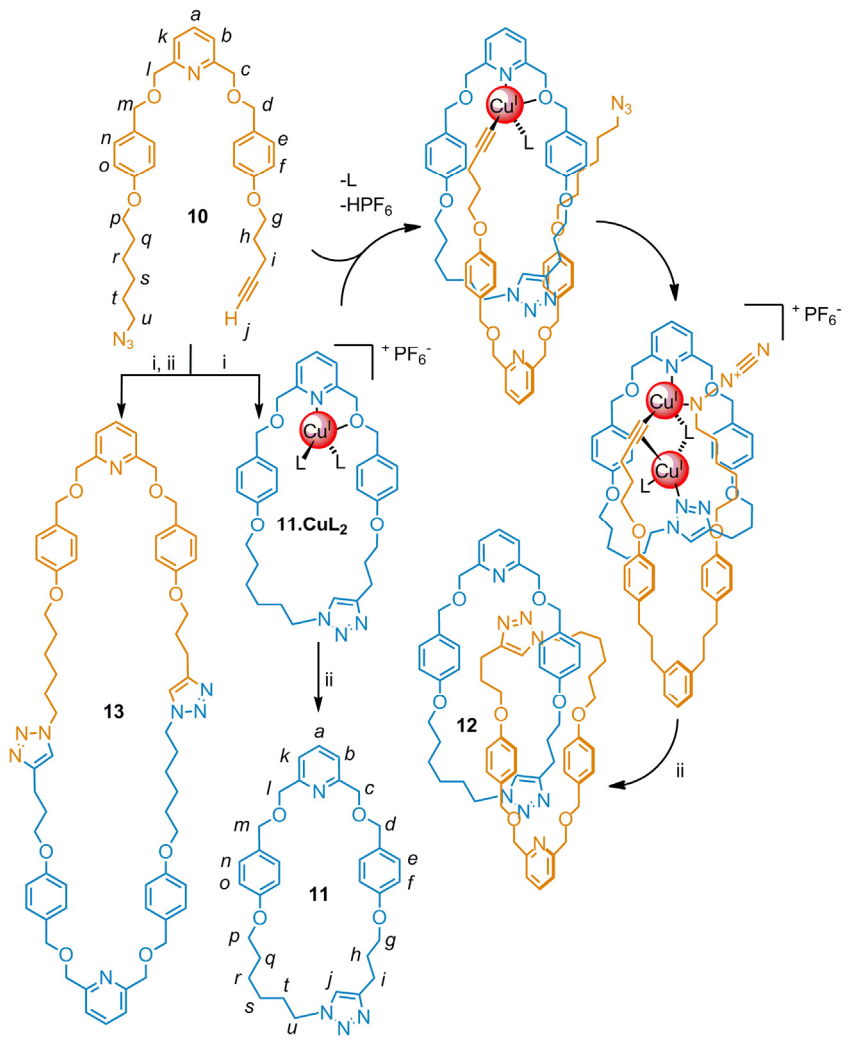
Figure 4.4. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) triazole macrocycle **8**, b) [2]catenane **9**, c) bipyridine macrocycle **1**. The assignments correspond to the lettering indicated for macrocycles **1** and **8** in Schemes 4.1 and 4.2 respectively.

4.2.3 Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Double Macrocyclization of Two Identical Acyclic Building Blocks

The active template reactions investigated so far (Schemes 4.1–4.3) featured a preformed macrocycle as one of the components and involved a single macrocyclization step (Figure 4.1a) leading to heterocircuit catenanes. We were interested to see whether it would be possible to extend this concept to an active template double macrocyclization strategy (Figure 4.1b) in which a homocircuit (both interlocked rings constitutionally identical) [2]catenane was assembled in one pot by two successive macrocyclization reactions (the final one, at least, having to be templated by the catalyst) of a single type of building block (Scheme 4.4).

Ligand **10** incorporates the terminal alkyne and azide groups necessary for the CuAAC reaction, together with a pyridine group for coordination to a Cu ion catalyzing the ring closure of another molecule of **10**. The covalent framework of the ligand was chosen to mimic macrocycle **5** and acyclic unit **6**, which combine effectively to give catenane in the single macrocyclization active template CuAAC reaction (Scheme 4.2).

Scheme 4.4. Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** from Azide-Alkyne **10**[a]



[a]Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 5 d. (ii) EDTA, NH_3(aq). L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of concentration on catenane yield, see Table 4.2.

Building block **10** was dissolved in $C_2H_4Cl_2$ with one-half of an equivalent of $[Cu(CH_3CN)_4](PF_6)$, and the solution was heated at 80 °C for 5 days (Scheme 4.4). The yield of [2]catenane proved to be highly dependent on the reaction concentration (Table 4.2), presumably a reflection of the delicate balance between various types of coordination complexes that can give rise to oligomers, noninterlocked macrocycles, or catenane. Carrying out the reaction at an initial 0.3 mM concentration of **10** gave a remarkable 46% yield of metal-free [2]catenane **12**, isolated after workup with a basic

EDTA solution and purification by column chromatography. Very little (<7% as compared to 46% [2]catenane) of noninterlocked macrocycles **11** and **13** were isolated from the reaction reported in Table 4.2, entry 5. It is intriguing that even at these relatively low concentrations the double macrocyclization reaction is more selective for the [2]catenane than the corresponding single macrocyclization employing pyridine macrocycle **5** and 1 equiv of the acyclic azide-alkyne building block **6** (Scheme 4.2 and Table 4.1, entry 2). A possible explanation could be that the second Cu^{I} ion involved in the mechanism of these reactions[3,9d] becomes coordinated to the triazole nitrogen of macrocycle **11**, resulting in a reaction geometry in which interlocking is significantly enhanced, as shown in Scheme 4.4. As the two Cu^{I} centers are linked via both a bridging ligand, L, and coordination to the alkyne, the azide is forced to approach the reactive center through the cavity of macrocycle **11** for the CuAAC reaction to occur, leading predominantly to catenane.

Table 4.2. Influence of Concentration on the Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** (Scheme 4.4). Half an equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to **10**. All reactions were performed in $C_2H_4Cl_2$ at 80 °C over 120 h.

Entry	[10] (mM)	Conversion to triazole products (%)	Ratio catenane 12: macrocycles 11 and 13	Yield of [2]catenane 10→12 (%)
1	15	>98	2:3	8
2	6	>98	2:3	16
3	3	>98	5:2	25
4	1	>98	3:1	30
5	0.3	>98	7:1	46
6	0.08	65	1:1	40
7	0.03	25	1:6	6

The structure of [2]catenane **12** was confirmed by mass spectrometry (fragmentation and MS-MS studies, *vide infra – Section 4.4.4*) and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of catenane **12** in $CDCl_3$ is shown in Figure 4.5b. The upfield shifts of the signals as compared to macrocycle **11** (Figure 4.5a) and building block **10**

(Figure 4.5c) show the same general trends found in the heterocircuit catenane produced by the single macrocyclization active template CuAAC reaction, **7** (Figure 4.3).

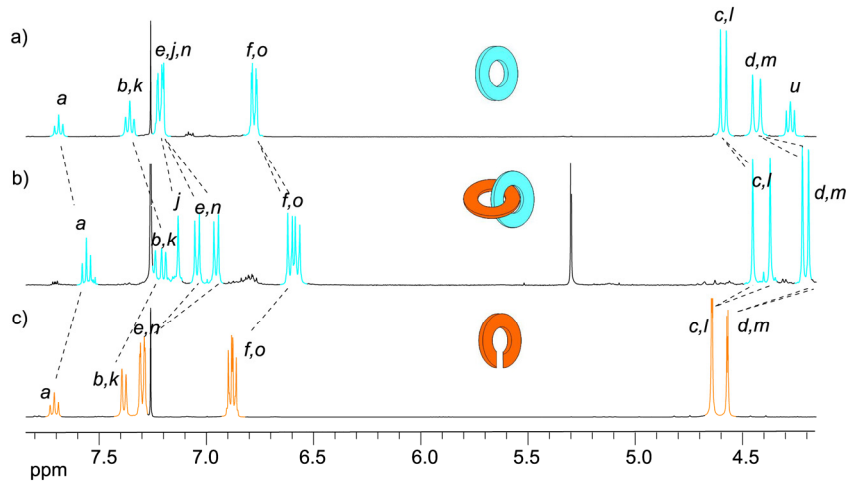


Figure 4.5. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) macrocycle **11**, b) [2]catenane **12**, c) azide-alkyne building block **10**. The assignments correspond to the lettering shown in Scheme 4.4.

4.3 Conclusions

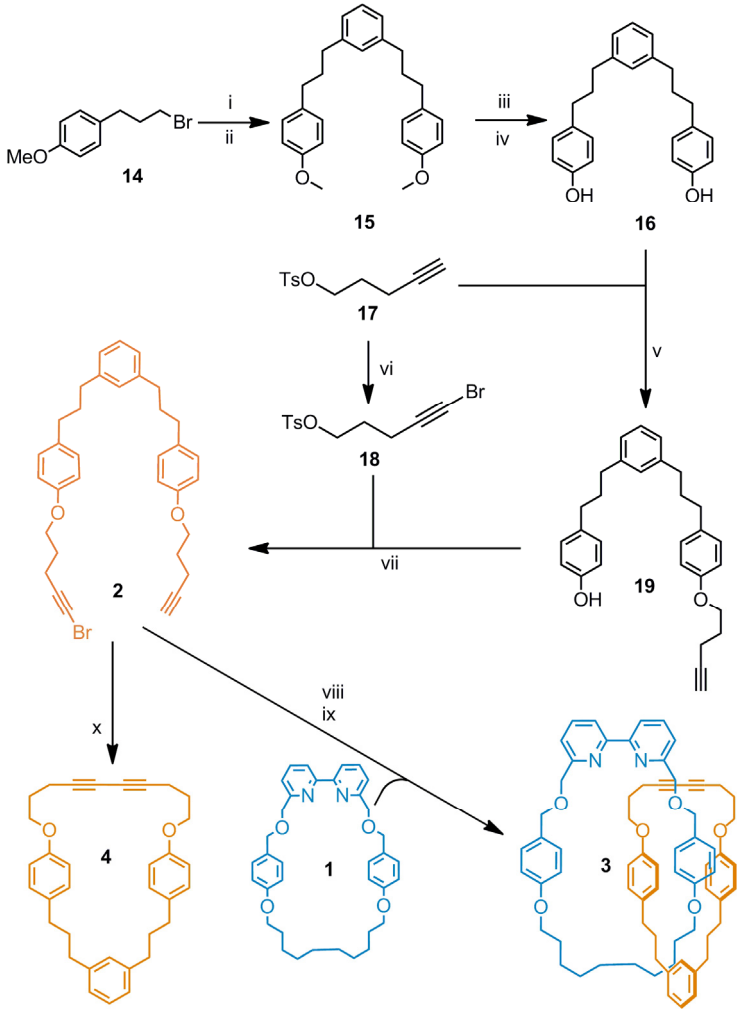
The work shown here shows that active template concept developed for rotaxanes can indeed be successfully extended to the more demanding requirements of catenane synthesis. Heterocircuit [2]catenanes were prepared in 21-53% yields through Cu^{I}-mediated active template single macrocyclization strategies employing the Cadiot-Chodkiewicz (forming a symmetrical bisacetylene-containing macrocycle) or CuAAC "click" reaction (forming an unsymmetrical triazole-containing macrocycle) and preformed monodentate or bidentate macrocyclic ligands. The CuAAC reaction could also be used to assemble homocircuit [2]catenanes from a single type of acyclic building block in a one-pot procedure in up to 46% yield, a remarkable catalytic assembly reaction notable for its selectivity for the interlocked architecture over noninterlocked macrocyclic products. The application of such strategies to higher order interlocked structures is currently under investigation in our laboratory.

4.4 Experimental Details

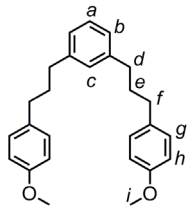
Bipyridyl macrocycle **1**,[9d] pyridyl macrocycle **5**,[14] 1-(3-bromo-propyl)-4-methoxy-benzene **14**,[17] toluene-4-sulfonic acid pent-4-ynyl ester **17**,[9d] 6-azido-hexan-1-ol **20**,[18] and diphenol **22**[9d] were prepared according to literature procedures.

4.4.1 Synthesis of Cadiot-Chodkiewicz Catenane 3

Scheme 4.5. Synthesis of [2]catenane **3**[a]

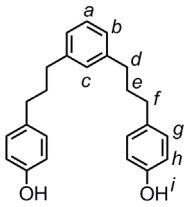


[a]Reagents and conditions: (i) Zn, I_2, NMP, rt → 80 °C, 4 h; (ii) 1,3-dibromobenzene, PEPPSI, LiBr, THF, rt, 2 h, 70% (over two steps); (iii) BBr_3, CH_2Cl_2, -78 °C → rt, 2 h; (iv) H_2O, rt, 10 min, 99% (over two steps); (v) K_2CO_3, DMF, 80 °C, 18 h, 42%; (vi) NBS, $AgNO_3$, acetone, rt, 2 h, 95%; (vii) Cs_2CO_3, DMF, 100 °C, 18 h, 93%; (viii) LiHMDS, THF, -78 °C, 30 min; (ix) CuI, THF, -78 °C → rt, 72 h, 21%; (x) LiHMDS, THF, -78 °C, 30 min; (xi) CuI, THF, -78 °C → rt, 7 days, 12%.



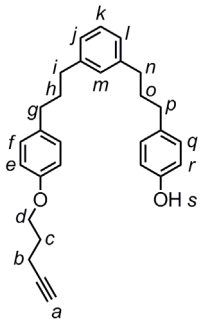
15

To a stirred suspension of Zn (0.49 g, 7.5 mmol, 3.5 eq.) in NMP (5 mL) at rt was added I_2 (64 mg, 0.25 mmol, 0.1 eq.) and the mixture stirred until the color of the iodine had disappeared (approximately 2 min). **14**[17] (1.1 g, 4.8 mmol, 2.2 eq.) was added and the reaction mixture was heated to 80 ºC for 4 h. After this time, the reaction mixture was cooled to rt and transferred to a flask containing LiBr (0.87 g, 10 mmol, 5 eq.), 1,5-dibromobenzene (0.51 g, 2.1 mmol, 1.0 eq.) and PEPPSI[19] (34 mg, 50 μmol, 0.03 eq.) dissolved in THF (5 mL). The reaction mixture was stirred for 2 h at rt, and then quenched with 1 M HCl (20 mL). The reaction was then extracted with Et_2O (3 × 50 mL) and the combined organic layers washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica (petrol-EtOAc 15:1) yielded the title compound **15** as a colorless oil (0.56 g, yield = 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.6, 1H, H_a), 7.10 (d, *J* = 7.6, 4H, H_g), 7.02-6.99 (m, 3H, H_{b+c}), 6.83 (d, *J* = 7.6, 4H, H_h), 3.79 (s, 6H, H_i), 2.64-2.56 (m, 8H, H_{d+f}), 1.96-1.88 (m, 4H, H_e); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 142.3, 134.4, 129.3, 128.6, 128.2, 125.8, 113.7, 55.3, 35.4, 34.6, 33.2. LRESI-MS: *m/z* = 375 $[M+H]^+$. HRESI-MS: *m/z* = 392.2565 $[M+NH_4]^+$ (calcd. for $C_{26}H_{34}O_2N$, 392.2584 $[M+NH_4]^+$).



16

To a solution of compound **15** (0.28 g, 0.75 mmol, 1 eq.) in CH_2Cl_2 (3 mL) at -78 ºC was added BBr_3 (1.1 g, 0.43 mL, 4.5 mmol, 6 eq.) and the reaction stirred at rt for 2 h. After this time, the reaction was quenched with distilled H_2O and the volume of solvent reduced *in vacuo*. Filtration gave diphenol **16** as a white solid, m.p. 62-64 ºC (0.26 g, yield = 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 7.6, 1H, H_a), 7.05 (d, *J* = 8.4, 4H, H_g), 7.01-6.97 (m, 3H, H_{b+c}), 6.74 (d, *J* = 8.4, 4H, H_h), 4.54 (s, 2H, H_i), 2.62-2.56 (m, 8H, H_{d+f}), 1.94-1.86 (m, 4H, H_e); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 142.3, 134.6, 129.5, 128.6, 128.2, 125.8, 115.1, 35.3, 34.6, 33.2. LRESI-MS: *m/z* = 345 [*M*-H]$^-$. HRESI-MS: *m/z* = 345.1857 [*M*-H]$^-$ (calcd. for $C_{24}H_{25}O_2$, 345.1860 [*M*-H]$^-$).

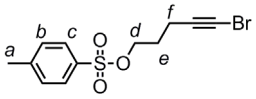


19

To a solution of diphenol **16** (2.2 g, 6.3 mmol, 1 eq.) and **17**[9d] (1.5 g, 6.3 mmol, 1 eq.) in DMF (13 mL) was added K_2CO_3 (1.8 g, 13 mmol, 2 eq.) and the suspension was heated at 80 °C for 18 h. After cooling, the solution was then quenched with 1 M HCl (20 mL), extracted into Et_2O (3 × 50 mL) and the combined organic extracts washed with brine (50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude oil was then purified by

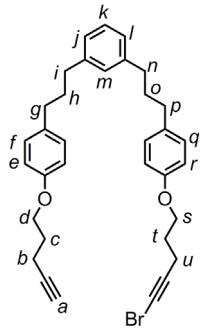
column chromatography on silica (CH_2Cl_2-EtOAc 20:1) to yield **19** as a colorless oil (1.1 g, yield = 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 7.6, 1H, H_k), 7.11 (d, *J* = 8.8, 2H, H_f), 7.06 (d, *J* = 8.4, 2H, H_q), 7.03-7.01 (m, 3H, H_{j+l+m}), 6.85 (d, *J* = 8.8, 2H, H_e), 6.76 (d, *J* = 8.4, 2H, H_r), 4.90 (s, 1H, H_s), 4.06 (t, *J* = 6.0, 2H, H_d), 2.64-2.58 (m, 8H, $H_{g+i+n+p}$), 2.45-2.40 (m, 2H, H_b), 2.04-1.97 (m, 3H, H_{a+c}), 1.96-1.89 (m, 4H, H_{h+o}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 153.4, 142.2 (x 2), 134.5, 134.4, 129.4, 129.2, 128.6, 128.1, 125.7 (x 2), 115.0, 114.3, 83.5, 68.7, 66.1, 35.3 (x 2), 34.5 (x 2), 33.1 (x 2), 28.2, 15.1. LRESI-MS: *m/z* = 411 [*M*-H]$^-$. HRESI-MS: *m/z* = 411.2319 [*M*-H]$^-$ (calcd. for $C_{29}H_{31}O_2$, 411.2330 [*M*-H]$^-$).

Toluene-4-sulfonic acid 5-bromo-pent-4-ynyl ester



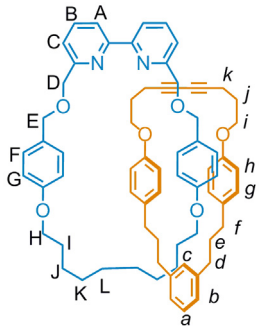
18

To a suspension of the alkyne **17**[9d] (0.48 g, 2.0 mmol, 1 eq.) and N-bromosuccinimide (0.39 g, 2.2 mmol, 1.1 eq.) in acetone (8 mL) was added $AgNO_3$ (34 mg, 0.20 mmol, 0.1 eq.), and the reaction stirred at rt for 2 h. The mixture was then diluted with petrol (b.p. 40-60 °C) and washed with H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (3 × 50 mL) and the combined organic fractions were then dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica (petrol-EtOAc 15:1) to yield **18** as a yellow oil (0.60 g, yield = 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0, 2H, H_c) , 7.35 (d, *J* = 8.0, 2H, H_b), 4.10 (t, *J* = 8.0, 2H, H_d) , 2.44 (s, 3H, H_a), 2.26 (t, *J* = 8.0, 2H, H_f), 1.85-1.79 (m, 2H, H_e); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 132.7, 130.0, 127.9, 78.0, 68.6, 39.3, 27.5, 21.7, 15.9. LRESI-MS: *m/z* = 317 [M^{79}Br+H]$^+$, 319 [M^{81}Br+H]$^+$. HRESI-MS: *m/z* = 316.9844 [M^{79}Br+H]$^+$ (calcd. for $C_{12}H_{14}{}^{79}BrO_3S$, 316.9847 [$M^{79}$Br+H]$^+$).



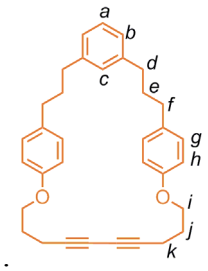
2

To a solution of **19** (0.30 g, 0.73 mmol, 1.0 eq.) and **18** (0.28 g, 0.88 mmol, 1.2 eq.) in DMF (20 mL) was added Cs_2CO_3 (0.94 g, 2.9 mmol, 4.0 eq.) and the resulting suspension heated to 100 °C for 18 h. After cooling, the reaction was poured into EtOAc (50 mL) and then quenched with 1 M HCl (20 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were then washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica (petrol-CH_2Cl_2 5:1) to yield **2** as a colorless oil (0.38 g, yield = 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 7.6, 1H, H_k), 7.09-7.07 (m, 4H, H_{f+q}), 7.01-6.99 (m, 3H, H_{j+l+m}), 6.83-6.81 (m, 4H, H_{e+r}), 4.06-4.01 (m, 4H, H_{d+s}), 2.62-2.57 (m, 8H, $H_{g+i+n+p}$), 2.44-2.38 (m, 4H, H_{b+u}), 2.02-1.87 (m, 9H, $H_{a+c+h+o+t}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 156.9, 142.3 (x 2), 134.5 (x 2), 129.3 (x 2), 128.6, 128.2, 125.8 (x 2), 114.3 (x 2), 83.6, 79.4, 68.8, 66.1 (x 2), 38.4, 35.3 (x 2), 34.5 (x 2), 33.2 (x 2), 28.2, 28.1, 16.5, 15.2. LRESI-MS: *m/z* = 556 $[M^{79}Br]^+$, 558 $[M^{81}Br]^+$. HRESI-MS: *m/z* = 556.1979 $[M^{79}Br]^+$ (calcd. for $C_{34}H_{37}{}^{79}BrO_2$, 556.1977 $[M^{79}Br]^+$).



3

To a solution of **2** (56 mg, 0.10 mmol 5 eq.) in THF (0.2 mL) at -78 °C was added LiHMDS (1.0 M in THF, 0.10 mL, 0.10 mmol, 5 eq.) and the mixture was stirred for 30 min at -78 °C, after which time the reaction mixture was transferred to a flask containing CuI (4.0 mg, 20 μmol, 1 eq.) and macrocycle **1** (11 mg, 20 μmol, 1 eq.) in THF (0.3 mL). The reaction mixture was then allowed to stir for a further 72 h at rt. After this time, the reaction was cooled to 0 °C and quenched by addition of 17.5% $NH_{3(aq)}$ saturated with EDTA (1 mL) and allowed to stir in air for 40 minutes, during which time the aqueous layer turned blue. The organic layer was separated, washed with brine and dried over $MgSO_4$. After removal of the solvents *in vacuo,* the resulting crude oil was purified by column chromatography on silica (CH_2Cl_2-acetonitrile 10:1) to yield **3** as a colorless oil (4.3 mg, yield = 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.7, 2H, H_A), 7.64 (t, *J* = 7.7, 2H, H_B), 7.35 (d, *J* = 7.7, 2H, H_C), 7.14-7.09 (m, 5H, H_{a+F}), 6.93-6.89 (m, 2H, H_b), 6.76 (d, *J* = 8.5, 4H, H_g), 6.70 (s, 1H, H_c), 6.66 (d, *J* = 8.6, 4H, H_G), 6.48 (d, *J* = 8.5, 4H, H_h), 4.60-4.58 (m, 8H, H_{D+E}), 3.75-3.67 (m, 8H, H_{i+H}), 2.40-2.34 (m, 8H, H_{d+f}), 2.30 (t, *J* = 6.1, 4H, H_k), 1.71-1.61 (m, 8H, H_{e+j}), 1.49-1.42 (m, 4H, H_I), 1.43-1.10 (m, 12H, H_{J+K+L}); ^{13}C NMR (200 MHz, $CDCl_3$): δ = 158.4, 158.1, 156.3, 155.1, 142.3, 136.7, 133.9, 129.5, 129.0, 127.8, 127.4, 125.5, 121.0, 119.4, 114.1 (x 2), 113.7, 76.0, 72.2, 67.4, 65.7, 64.6, 62.6, 34.9, 34.8, 34.6, 28.6, 28.5, 27.3, 25.4, 18.6, 15.1. LRESI-MS: *m/z* = 1044 $[M+H]^+$. HRFAB-MS: *m/z* = 1043.5951 $[M+H]^+$ (calcd. for $C_{70}H_{79}O_6N_2$, 1043.5938 $[M+H]^+$).

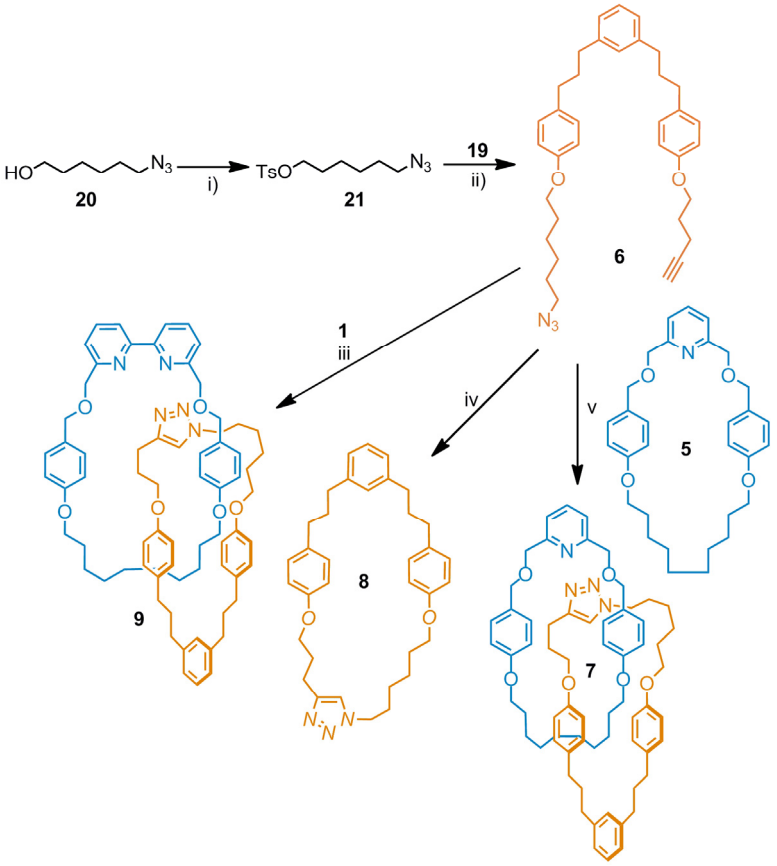


4

To a solution of **2** (22 mg, 40 µmol, 1 eq.) in THF (0.2 mL) at -78 °C was added LiHMDS (1.0 M in THF, 40 µL, 40 µmol, 1 eq.) and the mixture was stirred for 30 min at -78 °C, after which time the reaction mixture was transferred to a flask containing CuI (7.6 mg, 40 µmol, 1 eq.) in THF (0.6 mL). The reaction mixture was then allowed to stir for a further 7 days at rt. After this time, the reaction mixture was cooled to 0 °C and quenched by addition of 17.5% $NH_{3(aq)}$ saturated with EDTA (1 mL) and allowed to stir in air for 40 min, during which time the aqueous layer turned blue. The organic layer was separated, washed with brine and dried over $MgSO_4$. After removal of the solvents *in vacuo,* the resulting crude oil was purified by column chromatography on silica (petrol-EtOAc 50:1) to yield **4** as a colorless oil (2.2 mg, yield = 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.6, 1H, H_a), 7.08 (d, *J* = 8.4, 4H, H_g), 7.01-6.99 (m, 3H, H_{b+c}), 6.80 (d, *J* = 8.4, 4H, H_h), 4.01-3.98 (m, 4H, H_i), 2.62-2.56 (m, 8H, H_{d+f}), 2.48-2.44 (m, 4H, H_k), 2.00-1.86 (m, 8H, H_{j+e}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 142.2, 134.5, 129.2, 128.6, 128.1, 125.7, 114.3, 76.6, 66.0, 65.7, 35.3, 34.5, 33.2, 28.1, 16.0. LRESI-MS: *m/z* = 477 $[M+H]^+$. HRESI-MS; 477.2792 $[M+H]^+$ (calcd. for $C_{34}H_{37}O_2$, 477.2794 $[M+H]^+$).

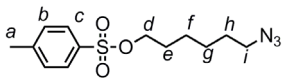
4.4.2 Synthesis of Heterocircuit "Click" Catenanes 7 and 9

Scheme 4.6. Synthesis of [2]catenanes **7** and **9**[a]



Reagents and conditions: (i) Et_3N, *p*-TsCl, CH_2Cl_2, 0 °C → rt, 18 h, 86%; (ii) K_2CO_3, DMF, 80 °C, 18 h, 34%; (iii) $[Cu(MeCN)_4]PF_6$, 1,2-dichloroethane, 80 °C, 170 h, 49%; (iv) $[Cu(MeCN)_4]PF_6$, 1,2-dichloroethane, 80 °C, 18 h, 41%; (v) $[Cu(MeCN)_4]PF_6$, 1,2-dichloroethane, 80 °C, 12 d, 53%.

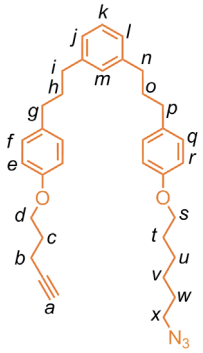
Toluene-4-sulfonic acid 6-azido-hexyl ester



21

To a solution of **20**[18] (1.80 g, 12.6 mmol, 1 eq.) and Et_3N (1.53 g, 2.10 mL, 15.1 mmol, 1.2 eq.) in CH_2Cl_2 (100 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.88 g, 15.1 mmol, 1.2 eq.) and the reaction allowed to stir at rt for 18 h. After this time, the reaction was filtered through a pad of celite, and the celite washed with EtOAC (50 mL). The combined filtrates were then washed with H_2O (50 mL) and the

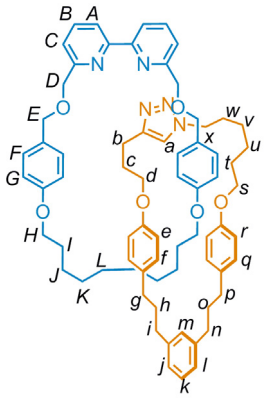
aqueous phase extracted with EtOAC (3 × 50 mL). The combined organic fractions were then washed with brine (50 mL) and dried ($MgSO_4$). After filtration and concentration under reduced pressure, the resulting crude oil was purified by column chromatography on silica (hexane-EtOAC 15:1) to yield **21** as a colorless oil (3.21 g, yield = 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0, 2H, H_c), 7.35 (d, *J* = 8.0, 2H, H_b), 4.10 (t, *J* = 6.4, 2H, H_d), 3.22 (t, *J* = 6.8, 2H, H_i) 2.45 (s, 3H, H_a), 1.68-1.61 (m, 2H, H_e), 1.57-1.51 (m, 2H, H_h), 1.34-1.31 (m, 4H, H_{f+g}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 133.1, 129.8, 127.9, 70.3, 51.2, 28.7, 28.6, 26.1, 25.0, 21.6. LRESI-MS: *m/z* = 298 $[M+H]^+$. HRESI-MS: *m/z* = 298.1226 $[M+H]^+$. (calcd. for $C_{13}H_{20}N_3O_3S$, 298.1225 $[M+H]^+$).



6

To a solution of **19** (0.21 g, 0.50 mmol, 1 eq.) and **21** (0.22 g, 0.75 mmol, 1.5 eq.) in DMF (1.5 mL) was added K_2CO_3 (0.21 g, 1.5 mmol, 3.0 eq.) and the suspension heated to 80 °C for 18 h. After cooling to rt, the reaction mixture was poured into EtOAc (50 mL) and quenched with 1 M HCl (20 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography on silica (petrol-EtOAc 20:1) to yield **6** as a colorless oil (90 mg, yield = 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 7.6, 1H, H_k), 7.10-7.06 (m, 4H, H_{f+q}), 7.00-6.99 (m, 3H, H_{j+l+m}), 6.84-6.80 (m, 4H, H_{e+r}), 4.04 (t, *J* = 6.0, 2H, H_d), 3.93 (t, *J* = 6.4, 2H, H_s), 3.28 (t, *J* = 6.8, 2H, H_x), 2.62-2.56 (m, 8H, $H_{g+i+n+p}$), 2.43-2.38 (m, 2H, H_b), 2.02-1.87 (m, 7H, $H_{a+c+h+o}$), 1.82-1.75 (m, 2H, H_t), 1.69-1.39 (m, 6H, H_{u+v+w}); ^{13}C

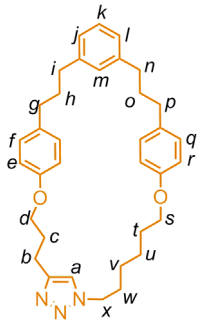
NMR (100 MHz, $CDCl_3$): δ = 157.1, 156.9, 142.3, 142.2, 134.4, 134.3, 129.2 (x 2), 128.5, 128.1, 125.7 (x 2), 114.3, 114.2, 83.5, 68.7, 67.6, 66.0, 51.3, 35.3 (x 2), 34.5 (x 2), 33.2 (x 2), 29.1, 28.7, 28.2, 26.4, 25.6, 15.1. LRESI-MS: *m/z* = 538 $[M+H]^+$. HRESI-MS: *m/z* = 537.3346 $[M]^+$ (calcd. for $C_{35}H_{43}N_3O_2$, 537.3355 $[M]^+$).



9

To a solution of macrocycle **1** (24 mg, 42 µmol, 1 eq.) and $[Cu(MeCN)_4]PF_6$ (16 mg, 42 µmol, 1 eq.) in 1,2-dichloroethane (9 mL) was added compound **6** (95 mg, 0.18 mmol, 4 eq.) and the reaction mixture heated to 80 °C for 170 h. After this time, the reaction mixture was allowed to cool to rt and 17.5% $NH_{3(aq)}$ saturated with EDTA (9 mL) was added and the resulting mixture stirred vigorously for 10 min. The phases were separated and the organic phase was diluted with CH_2Cl_2 (20 mL) then washed with 17.5% $NH_{3(aq)}$ saturated with EDTA (30 mL), H_2O (3 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1. CH_2Cl_2, 2. CH_2Cl_2 with 5→20% CH_3CN) to give catenane **9** as a colorless film (23 mg, 49%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.6, 2H, H_A), 7.59 (t, *J* = 7.6, 2H, H_B), 7.30 (d, *J* = 7.6, 2H, H_C), 7.11 (t, *J* = 7.8, 1H, H_k), 6.95-6.81 (m, 11H, $H_{a+f+j+l+q+F}$), 6.66 (d, *J* = 8.6, 2H, $H_{(e\ or\ r)}$), 6.61 (d, *J* = 8.6, 2H, $H_{(e\ or\ r)}$), 6.49-6.44 (m, 5H, H_{m+G}), 4.50 (s, 4H, H_D), 4.44 (d, *J* = 1.5, 4H, H_E), 3.72-3.64 (m, 10H, $H_{d+s+x+H}$), 2.79-2.75 (m, 2H, H_b), 2.53-2.48 (m, 2H, $H_{(g\ or\ p)}$), 2.42-2.31 (m, 6H, $H_{(g\ or\ p)+i+n}$), 1.99-1.97 (m, 2H, H_c), 1.71-

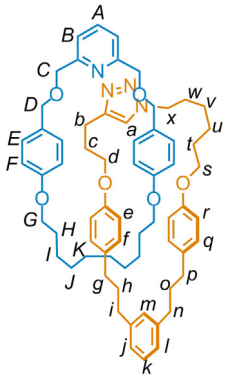
1.63 (m, 2H, $H_{(h\ or\ o)}$), 1.59-1.49 (m, 6H, $H_{(h\ or\ o)+l}$), 1.42-1.15 (m, 16H, $H_{t+w+J+K+L}$), 1.13-1.02 (m, 4H, H_{u+v}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 158.2, 156.9, 156.7, 155.4, 146.0, 142.4, 142.3, 142.2, 136.9, 134.1, 134.0, 129.5, 129.3, 129.2 (x 2), 128.0, 127.6, 125.7 (x 2), 121.2, 119.7, 114.2, 114.1, 113.9, 72.1, 71.9, 67.5, 66.5, 65.1, 49.5, 35.5, 35.3, 35.1, 35.0, 34.5, 33.7, 33.4, 33.2, 30.1, 29.3, 28.8, 28.7, 28.1 (x 2), 25.7, 21.2. LRESI-MS: *m/z* = 1105 $[M]^+$ HRESI-MS: *m/z* = 1104.6571 $[M]^+$ (calcd. for $C_{71}H_{86}N_5O_6$, 1104.6578 $[M]^+$).



8

A solution of **6** (0.54 g, 1.0 mmol, 1 eq.) and $[Cu(MeCN)_4]PF_6$ (0.37 g, 1.0 mmol, 1 eq.) in 1,2-dichloroethane (15 mL) was stirred at 80 °C for 18 h. After this time, the reaction mixture was allowed to cool to rt and 17.5% $NH_{3(aq)}$ saturated with EDTA (15 mL) was added and the resulting mixture stirred vigorously for 1 h. The phases were separated and the organic phase was diluted with CH_2Cl_2 (20 mL) then washed with 17.5% $NH_{3(aq)}$ saturated with EDTA (30 mL), H_2O (3 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude oil was purified by column chromatography on silica (CH_2Cl_2-acetonitrile 30:1) to yield **8** as a colorless oil (0.22 g, yield = 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1H, H_a), 7.20 (t, *J* = 7.6, 1H, H_k), 7.06-7.01 (m, 6H, $H_{f+j+l+q}$), 6.86 (s, 1H, H_m), 6.78-6.75 (m, 4H, H_{e+r}), 4.29 (t, *J* = 7.2, 2H, H_x), 3.94-3.88 (m, 4H, H_{d+s}), 2.92 (t, *J* = 6.7, 2H, H_b), 2.62-2.53 (m, 8H, $H_{g+i+n+p}$), 2.18-2.10 (m, 2H, H_c), 1.92-1.83 (m, 6H, H_{h+o+w}), 1.77-1.70 (m, 2H, H_t), 1.52-1.44 (m, 2H, H_u), 1.38-1.31 (m, 2H, H_v); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (x 2), 146.7, 142.2, 142.1, 134.3, 134.2, 129.3, 129.2, 128.1 (x 2), 125.9, 125.8, 121.2, 114.3, 114.2, 67.2, 65.8, 49.9, 35.3, 34.9,

34.5, 34.3, 33.2, 33.1, 30.1, 28.5, 28.3, 25.7, 25.3, 21.5. LRESI-MS: *m/z* = 538 $[M+H]^+$. HRESI-MS: *m/z* = 538.3421 $[M+H]^+$ (calcd. for $C_{35}H_{44}N_3O_2$, 538.3434 $[M+H]^+$).



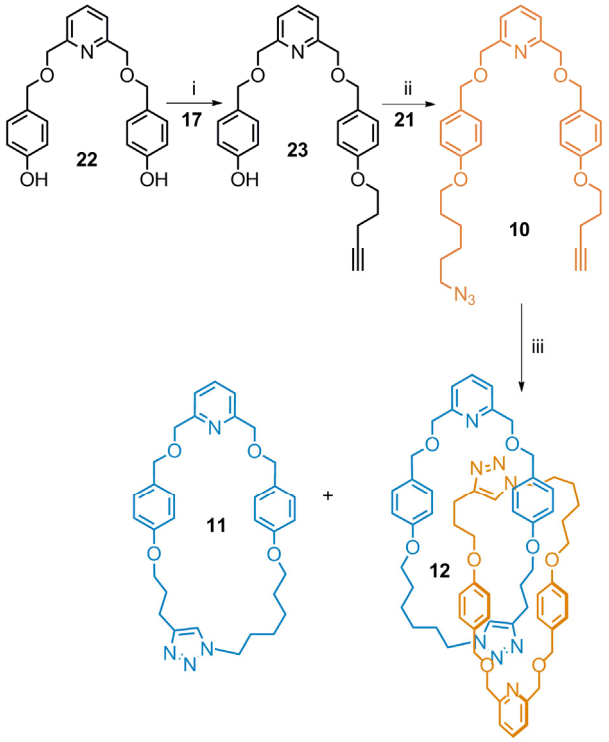
7

A solution containing macrocycle **5**[14] (16 mg, 33 µmol, 1 eq.), compound **6** (86 mg, 160 µmol, 5 eq.) and $[Cu(MeCN)_4]PF_6$ (12 mg, 33 µmol, 1 eq.) in degassed 1,2-dichoroethane (26 mL) was heated to 80 ºC for 12 days. The reaction mixture was then allowed to cool to rt before being washed with a saturated aqueous solution of EDTA/K_2CO_3 (20 mL). The layers were then separated and the aqueous fraction extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were then washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow residue, which was purified by flash column chromatography on silica (10% CH_3CN in CH_2Cl_2, followed by 10% CH_3CN in CH_2Cl_2 with 2% methanol) to give **7** as a pale yellow oil (18 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 7.7, 1H, H_A), 7.22 (d, *J* = 7.7, 2H, H_B), 7.13 (t, *J* = 7.5, 1H, H_k), 7.00-6.86 (m, 11H, $H_{a+f+j+l+q+E}$), 6.70-6.65 (m, 4H, H_{e+r}), 6.54-6.51 (m, 5H, H_{m+F}), 4.42-4.34 (m, 4H, H_C), 4.17 (s, 4H, H_D), 3.78-3.73 (m, 6H, H_{d+G}), 3.68 (t, *J* = 5.7, 2H, H_s), 3.59-3.55 (m, 2H, H_x), 2.79 (t, *J* = 7.5, 2H, H_b), 2.57-2.53 (m, 2H, $H_{(g\ or\ p)}$), 2.45-2.36 (m, 6H, $H_{(g\ or\ p)+i+n}$), 2.04-1.98 (m, 2H, H_c), 1.76-1.70 (m, 2H, $H_{(h\ or\ o)}$), 1.63-1.56 (m, 6H, $H_{(h\ or\ o)+H}$), 1.43-1.36 (m, 2H, H_t), 1.32-1.19 (m, 6H, H_{w+I}), 1.15-0.98 (m, 10H, H_{u+J+K}), 0.81-0.71 (m, 2H, H_v); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 157.5, 156.9, 156.7, 145.9, 142.4, 142.3, 136.8, 134.1, 134.0, 129.9, 129.3, 129.1, 129.0, 128.0, 127.6,

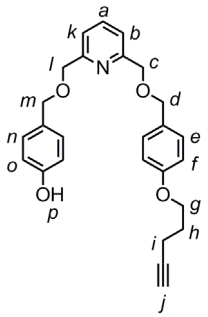
125.7, 125.5, 121.4, 119.3, 114.3, 114.1, 114.0, 72.2, 70.6, 66.9, 66.6, 65.2, 49.4, 35.5, 35.0 (x 2), 33.8, 33.4, 29.9, 29.6, 28.7, 28.5 (x 2), 28.1 (x 2), 25.6, 25.3, 24.9, 21.2. LRESI-MS: *m/z* = 1028 $[M+H]^+$ HRESI-MS: *m/z* = 1027.6336 $[M+H]^+$ (calcd. for $C_{66}H_{83}N_4O_6$, 1027.6313 $[M+H]^+$).

4.4.3 Synthesis of Homocircuit "Click" Catenane 12

Scheme 4.7. Synthesis of [2]catenane **12**[a]

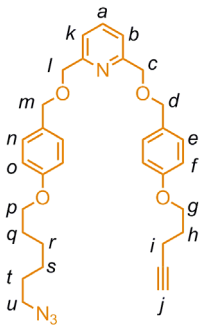


Reagents and conditions: (i) Cs_2CO_3, DMF, 55 °C, 3 h, 40%; (ii) Cs_2CO_3, DMF, 55 °C, 18 h, 96%; (iii) $[Cu(MeCN)_4]PF_6$, 1,2-dichloroethane, 80 °C, 120 h, 46% (**12**) and 6% (**11**).



23

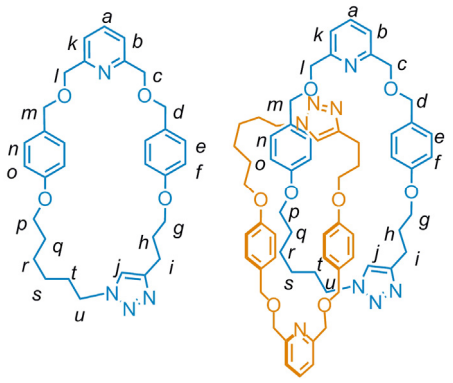
17[9d] (678 mg, 2.85 mmol, 1 eq.) was added to a solution of diphenol **22**[9d] (1.00 g, 2.85 mmol, 1 eq.) and Cs_2CO_3 (1.39 g, 4.27 mmol, 1.5 eq.) in DMF (25 mL) and the reaction mixture heated to 55 °C for 3 h. The reaction mixture was then allowed to cool to rt and EtOAc (200 mL) and H_2O (200 mL) were added. The phases were separated and the organic phase was washed with H_2O (3 x 200 mL) and brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1. CH_2Cl_2, 2. CH_2Cl_2 with 10→20% EtOAc) to give alkyne **23** (474 mg, 40%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (t, *J* = 7.7, 1H, H_a), 7.43-7.41 (m, 2H, H_{b+k}), 7.27 (d, *J* = 8.5, 2H, H_e), 7.16 (d, *J* = 8.5, 2H, H_n), 6.86 (d, *J* = 8.5, 2H, H_f), 6.72 (d, *J* = 8.5, 2H, H_o), 4.65 (s, 2H, $H_{(c\ or\ l)}$), 4.62 (s, 2H, $H_{(c\ or\ l)}$), 4.54 (m, 4H, H_{d+m}), 4.06 (t, *J* = 6.1, 2H, H_g), 2.40 (dt, J_1 = 7.0, J_2 = 2.6, 2H, H_i), 2.07-1.97 (m, 3H, H_{h+j}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 157.7 (x 2), 155.9, 137.8, 129.9, 129.8, 129.5, 129.0, 120.3 (x 2), 115.2, 114.4, 83.4, 72.7, 72.6, 72.1, 71.7, 68.8, 66.0, 28.1, 15.1. LRESI-MS: *m/z* = 417 $[M]^+$. HRESI-MS: *m/z* = 418.2021 $[M+H]^+$ (calc. for $C_{26}H_{28}O_4N_1$, 418.2013 $[M+H]^+$).



10

21 (267 mg, 898 µmol, 1.5 eq.) was added to a solution of phenol **23** (250 mg, 600 µmol, 1 eq.) and Cs_2CO_3 (586 mg, 1.80 mmol, 3 eq.) in DMF (6 mL) and the reaction mixture heated at 55 °C for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (40 mL) and H_2O (40 mL) were added. The phases were separated and the organic phase was washed with H_2O (3 x 40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified

by flash column chromatography on silica (1. CH_2Cl_2, 2. 9:1 CH_2Cl_2-EtOAc) to give **10** (313 mg, 96%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (t, *J* = 7.7, 1H, H_a), 7.39-7.37 (m, 2H, H_{b+k}), 7.32-7.28 (m, 4H, H_{e+n}), 6.91-6.85 (m, 4H, H_{f+o}), 4.64 (s, 4H, H_{c+l}), 4.57 (s, 4H, H_{d+m}), 4.07 (t, *J* = 6.1, 2H, H_g), 3.96 (t, *J* = 6.4, 2H, H_p), 3.28 (t, *J* = 6.9, 2H, H_u), 2.41 (dt, J_1 = 7.0, J_2 = 2.6, 2H, H_i), 2.05-1.95 (m, 3H, H_{h+j}), 1.83-1-75 (m, 2H, H_q), 1.68-1.59 (m, 2H, H_t), 1.55-1.38 (m, 4H, H_{r+s}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 158.5, 157.9 (x 2), 130.0, 129.8, 129.5 (x 2), 119.9, 114.4 (x 2), 114.3 (x 2), 83.4, 72.7 (x 2), 72.6 (x 2), 68.8, 67.6, 66.1, 51.3, 29.0, 28.7, 28.1, 26.4, 25.6, 15.1. LRESI-MS: *m/z* = 543 $[M+H]^+$. HRESI-MS: *m/z* = 543.2955 $[M+H]^+$ (calc. for $C_{32}H_{39}O_4N_4$, 543.2971 $[M+H]^+$).



11 **12**

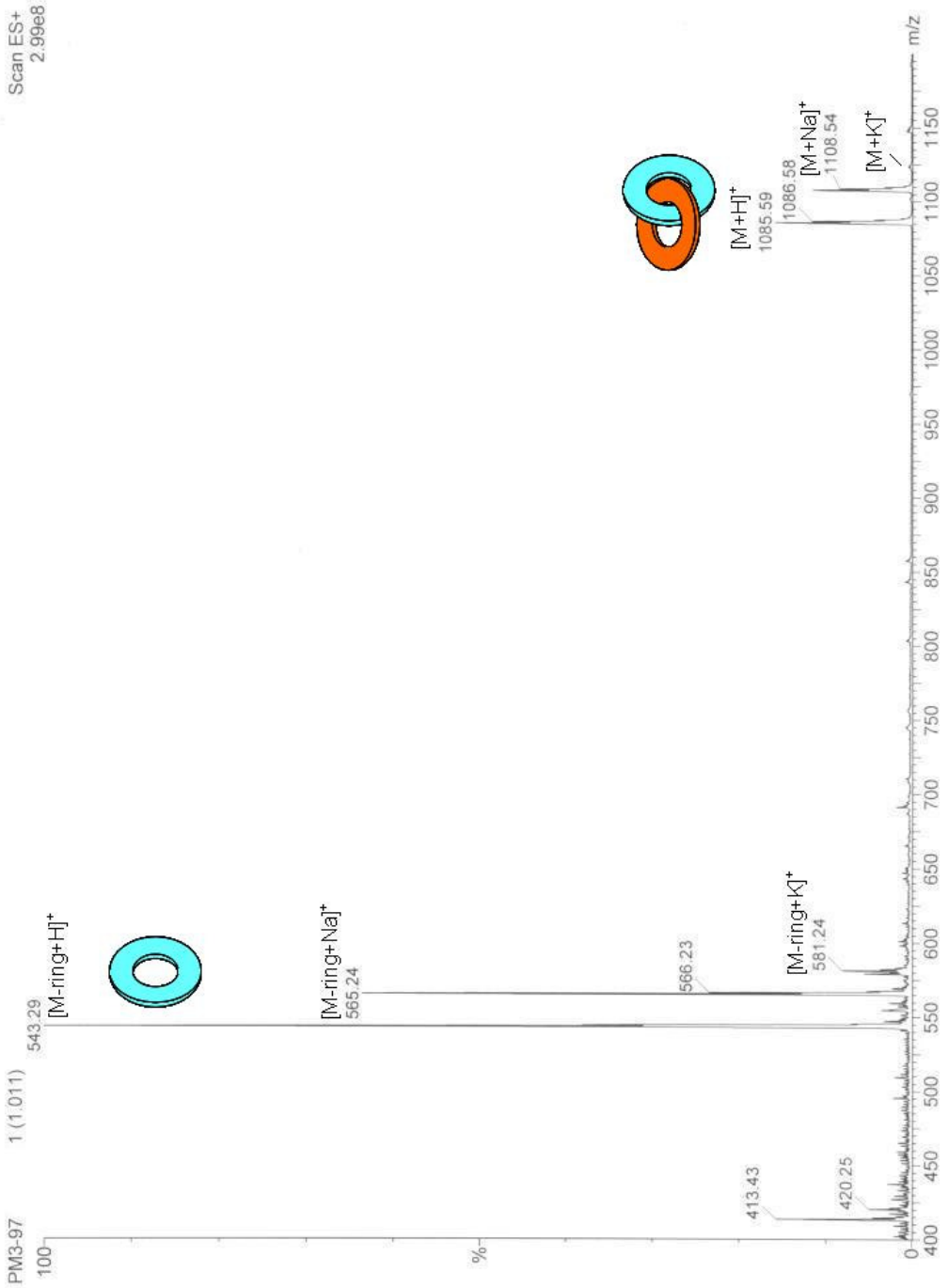
$[Cu(MeCN)_4]PF_6$ (17 mg, 46 µmol, 0.5 eq.) was added to a solution of compound **10** (50 mg, 92 µmol, 1 eq.) in 1,2-dichloroethane (240 mL) and the reaction mixture heated at 80 °C for 120 h. After this time, the reaction mixture was allowed to cool to rt and 17.5% $NH_{3(aq)}$ saturated with EDTA (240 mL) was added and mixture stirred vigorously for 10 min. The phases were separated and the organic phase was washed with 17.5% $NH_{3(aq)}$ saturated with EDTA (240 mL), H_2O (3 x 240 mL) and brine (240 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica (1. EtOAc, 2. EtOAc with 2→5% acetone) to give catenane **12** (23 mg, 46%) as a yellow resin and macrocycle **11** (3 mg, 6%) as a colorless oil.

Catenane 12: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (t, *J* = 7.7, 2H, H_a), 7.26-7.18 (m, 4H, H_{b+k}), 7.13 (s, 2H, H_j), 7.04 (d, *J* = 8.5, 4H, $H_{(e\ or\ n)}$), 6.95 (d, *J* = 8.5, 4H, $H_{(e\ or\ n)}$), 6.63-6.56 (m, 8H, H_{f+o}), 4.45 (s, 4H, $H_{(c\ or\ l)}$), 4.37 (s, 4H, $H_{(c\ or\ l)}$), 4.22-4.19 (m, 8H, H_{d+m}), 3.85-3.80 (m, 4H, H_u), 3.75-3.71 (m, 8H, H_{g+p}), 2.75 (t, *J* = 6.5, 4H, H_i), 2.00-1.92 (m, 4H, H_h), 1.55-1.45 (m, 8H, H_{q+t}), 1.29-1.19 (m, 4H, H_s), 1.08-0.98 (m, 4H, H_r); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 158.3, 157.5, 157.3, 146.0, 134.1, 129.9, 129.6, 129.4, 129.2, 121.8, 119.8, 119.6, 114.1, 114.0, 72.2 (x 2), 71.3, 70.7, 66.8, 65.5, 49.5, 30.0, 28.1 (x 2), 25.4, 25.0, 21.2. LRESI-MS: *m/z* = 1086 $[M+H]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 1085.5853 $[M+H]^+$ (calc. for $C_{64}H_{77}O_8N_8$, 1085.5864 $[M+H]^+$).

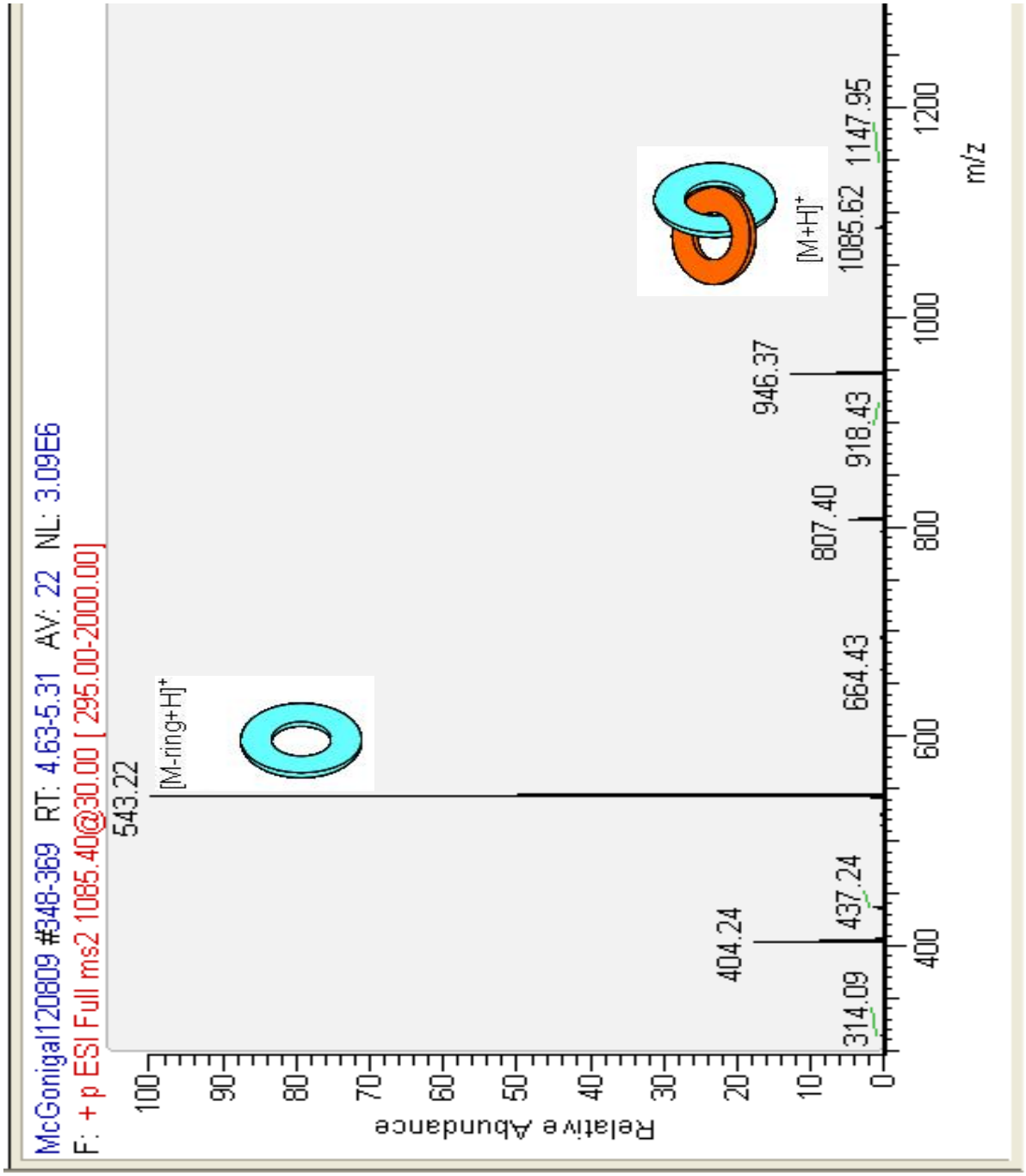
Macrocycle 11: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (t, *J* = 7.7, 1H, H_a), 7.38-7.34 (m, 2H, H_{b+k}), 7.24-7.19 (m, 5H, H_{e+j+n}), 6.78 (dd, J_1 = 8.6, J_2 = 1.7, 4H, H_{f+o}), 4.60-4.58 (m, 4H, H_{c+l}), 4.44-4.42 (m, 4H, H_{d+m}), 4.30-4.25 (m, 2H, H_u), 3.94 (t, *J* = 5.9, 2H, H_p), 3.85 (t, *J* = 6.0, 2H, H_g), 2.91 (t, *J* = 6.7, 2H, H_i), 2.16-2.08 (m, 2H, H_h), 1.92-1-82 (m, 2H, H_t), 1.77-1.69 (m, 2H, H_q), 1.52-1.43 (m, 2H, H_r), 1.38-1.31 (m, 2H, H_s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 158.5, 157.9, 157.6, 146.4, 137.1, 130.0, 129.8, 129.6, 129.4, 121.3, 120.1, 119.9, 114.3, 114.1, 72.5, 72.4, 71.8, 71.1, 66.9, 65.4, 50.0, 30.4, 28.3, 28.2, 25.7, 25.2, 21.3. LRESI-MS: *m/z* = 543 $[M+H]^+$; HRESI-MS: *m/z* = 543.2984 $[M+H]^+$ (calc. for $C_{32}H_{39}O_4N_4$, 543.2971 $[M+H]^+$).

4.4.4 Fragmentation Data of Catenane 12

LRMS Fragmentation Data



MS-MS Fragmentation Data



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16. In the case of the bidentate bipyridyl ligand **1**, the intermediate Cu(I) species in which the ligand, alkyne and azide are all complexed is proposed to be mono-metallic whereas a bi-metallic intermediate has been proposed for the CuAAC reaction involving ligand **5** (*see Scheme 4.2*).

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CHAPT. 5 | ACTIVE METAL TEMPLATE SYNTHESIS OF A TREFOIL KNOT

Synopsis

This Chapter describes studies towards the expansion of the AMT concept to the synthesis of a molecular trefoil knot. The strategy presented aims to make use of two Cu^{I} ions that work in tandem to entangle an acyclic building block and covalently capture the knotted architecture by an AMT reaction. The acyclic ligand designed to undergo this transformation incorporates three binding sites, two bipyridyl sites to chelate one Cu^{I} ion and a pyridyl site to retain the second Cu^{I} center, capable of mediating a CuAAC 'click' reaction.

Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Dr. Mark Symes and Dr. Stephen Goldup conceived of the overall project idea, Michael Zengerle and Jhenyi Wu developed the early stages of the synthetic route to ligand **1** which were repeated by the Author. The Author developed the majority of the synthesis towards ligand **1** and undertook all studies into the AMT knot forming reaction and subsequent analysis reported here. The Author also wishes to thank Marius Kroll for assistance with size exclusion chromatography.

5.1 Introduction

The development of supramolecular template strategies has allowed access to a wide variety of topologically complex molecules.[1] MIMs with multiple components such as rotaxanes and catenanes have flourished however there are relatively few examples of the single component molecular knots.[2] The most topologically simple interlocked knot, the trefoil knot, has been observed in DNA,[3] proteins,[4] and synthetic polymers[5] and remains the only small molecule prime knot to be successfully synthesized to date.[6] Pioneering work by Sauvage and co-workers[7] made use of ligand preorganization around two tetrahedral Cu^{I} centers as the key non-covalent template interaction in the preparation of the first synthetic molecular knot. Donor–acceptor interactions,[8] Watson–Crick base pairing,[9] hydrogen bonding[10] and ligand folding around an octahedral metal template[11] have also been utilized to hold precursors in the desired spatial orientation prior to covalent capture of a knotted architecture.

We have recently introduced a new strategy for the synthesis of mechanically bonded structures, the AMT methodology.[12] The central feature of this approach is that a macrocycle-bound metal ion plays a dual role, simultaneously acting as a template to entwine two or more components while also mediating bond formation to covalently trap the interlocked architecture.[13] The metal ion must be bound endotopically within the macrocylic cavity so as to promote interlocking upon covalent bond formation between two suitably functionalized "half-thread" units (rotaxane synthesis[13a–g,j–l]) or macrocyclization of a linear unit with two functional end groups (catenane synthesis[13h,i]). The general strategy has proven to be an efficient means by which to obtain interlocked molecules and is compatible with a number of different transition metal-mediated reactions. Macrobicyclic-[3]rotaxanes,[13j] alkyl chain rotaxanes[13l] and molecular shuttles with weak intercomponents interactions[13g] have been successfully attained via AMT reactions demonstrating the potential for this methodology to be used in the synthesis of hard-to-access structures. Herein we report the application of the AMT approach to the synthesis of the world's smallest trefoil knot.

5.2 Results and Discussion

We envisaged a system whereby a suitable ligand could be geometrically manipulated and knotted by two multi-functional Cu^{I} ions (Figure 5.1). Firstly, two cross-over points could be induced by chelation of two bidentate binding sites around the tetrahedral coordination sphere of one of the two metal centers, in a manner reminiscent of Sauvage's original trefoil knot synthesis.[7] The second Cu^{I} ion, bound to a monodentate site, could then perform the twofold task of gathering both functional end groups and catalyzing bond formation to covalently capture the kinetically stable entanglement.

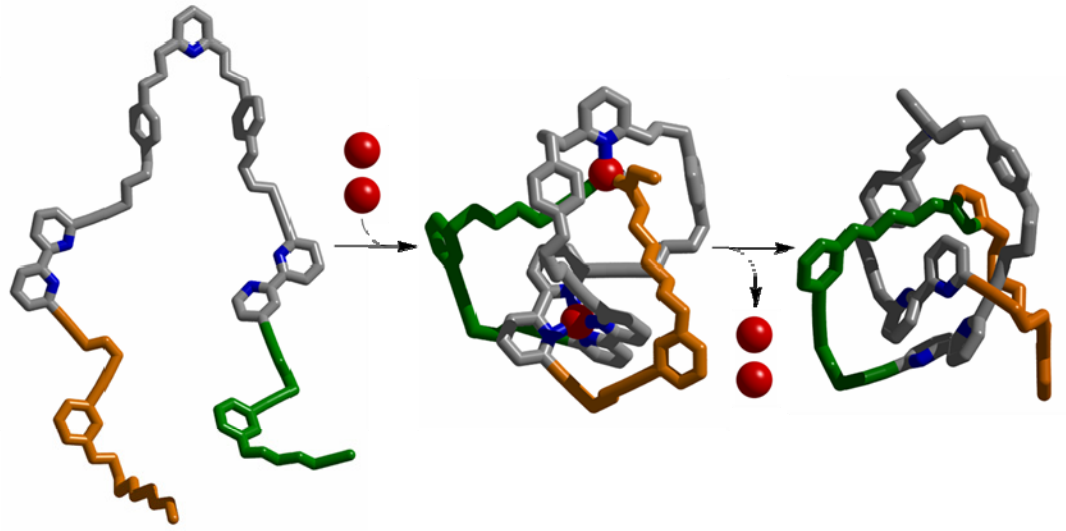
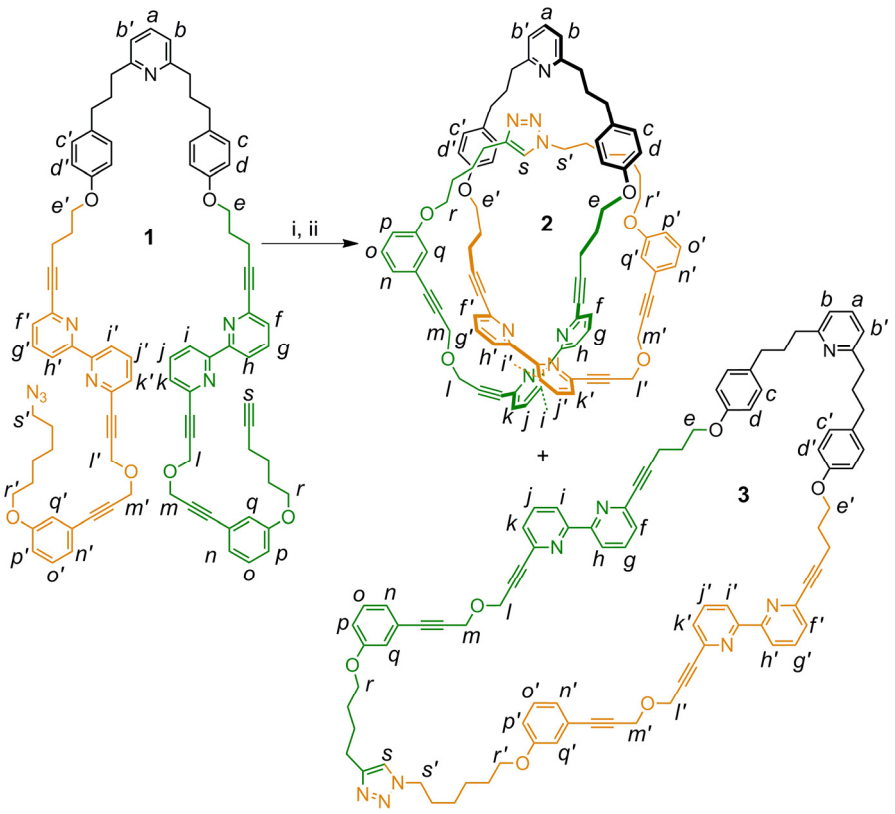


Figure 5.1. Schematic representation of the active template synthesis of a trefoil knot. A ligand with one monodentate and two bidentate binding sites (blue) and two functional end groups (orange and green) is knotted by two copper ions (red). One copper ion creates two cross-over points via coordination to the bidentate binding sites; the other simultaneously directs and mediates an active template CuAAC 'click' reaction to covalently capture the knotted geometry.

Ligand **1** (Scheme 5.1) was designed to incorporate the desired Cu^{I} binding sites and functional end groups and synthesized in 9 steps (*vide infra – Section 5.4*). The ligand comprises three binding sites, two bipyridyl sites intended to create a cross-over point by chelation of a Cu^{I} ion and a pyridyl site to retain the 'active' metal center. The AMT CuAAC 'click' reaction[13a,c] was selected as previous investigations have shown that the specific reaction preferences of the terminal alkyne and azide functionalities

make this transformation an ideal candidate for use in AMT macrocyclization reactions.[13i] Molecular modeling[14] was used to determine the optimal length of the alkyl chain 'spacers' between the functional end groups and Cu^{I} binding sites.

Scheme 5.1. AMT synthesis of trefoil knot **2**.[a]



[a] Reagents and conditions: (i) $CHCl_3$–CH_3NO_2 (4:1), $[Cu(CH_3CN)_4]PF_6$ (1.5 equiv.), 60 °C, 96 h; (ii) Na_2EDTA, NH_3(aq). **2** – 24%, **3** – 10%.

During previous investigations we found that the AMT CuAAC reaction tolerates a range of reaction media, however the highest yields were obtained in halogenated solvents.[13c] Accordingly, we initially probed conditions for the knotting reaction of ligand **1** (Scheme 5.1) in dichloromethane, chloroform and 1,2-dichloroethane. In this case however, we observed that upon addition of $[Cu(CH_3CN)_4]PF_6$ to a dilute solution of **1** in halogenated solvent, a precipitate was formed instantly.[15] In order to find an appropriate reaction medium we screened a number of solvent mixtures, leading us to an optimized mixture of chloroform–nitromethane 4:1 which effectively retained reagents in solution during the course of the reaction. Carrying out the AMT

reaction in this solvent mixture at optimized concentration (1.5 mM) with 1.5 equivalents of $[Cu(CH_3CN)_4]PF_6$ at 60 °C, we detected complete consumption of **1** by NMR of the crude reaction mixture after 4 days.

After demetallation with a basic Na_2EDTA-NH_3 solution, analysis of the reaction mixture by reverse phase HPLC showed several species were present (Figure 5.2). LCMS analysis revealed that the peaks with retention times of less than 10 minutes (Figure 5.2, green) correspond to low molecular weight degradation products whereas species that eluted after 20 minutes (Figure 5.2, orange) were oligomeric by-products derived from intermolecular cycloaddition reactions. Flanked by these undesired by-products, the two species that eluted after 12.6 and 16.5 minutes (Figure 5.2, blue) both displayed a molecular ion peak at *m/z* = 1362, the molecular weight of the target trefoil knot **2** or macrocycle **3**.

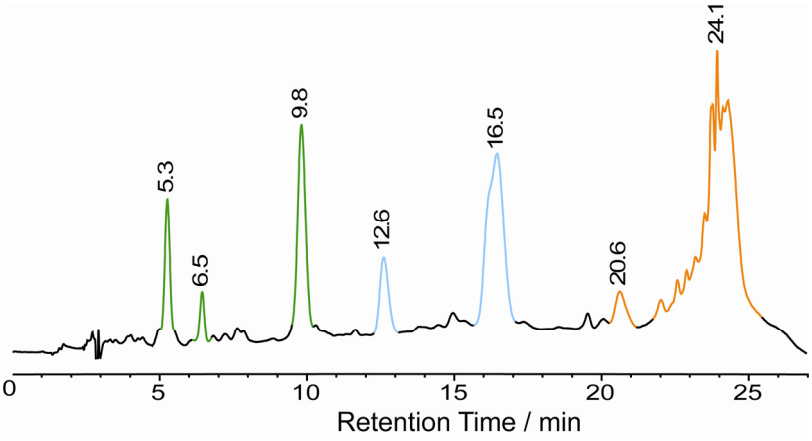


Figure 5.2. Reverse phase HPLC trace of the crude reaction mixture obtained after the AMT knotting reaction (Scheme 5.1). Peaks with a retention time of <10 min were assigned as degradation products (green), oligomeric species eluted after 20 min (orange) and peaks tentatively assigned as macrocycle **3** and trefoil knot **2** were observed after 12.6 min and 16.5 min respectively (blue).

Separation of the components of the reaction mixture was achieved using a combination of size exclusion chromatography and preparative HPLC. Size exclusion allowed facile removal of the oligomeric by-products which were otherwise problematic, streaking on preparative scale reverse or normal phase silica chromatography. We were then able to isolate the two products—tentatively assigned

as trefoil knot **2** and macrocycle **3** after comparison of their ^{1}H NMR spectra (Figure 5.3)—by subjecting the partly refined mixture to reverse phase preparative HPLC.

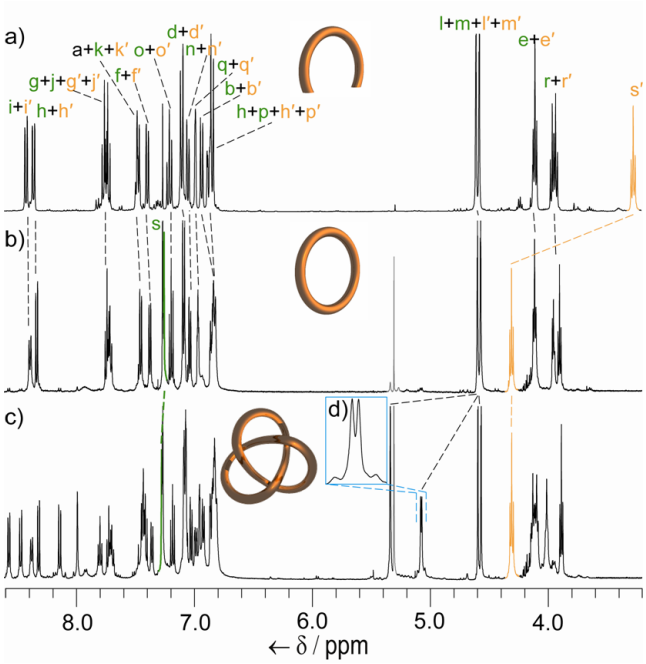


Figure 5.3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) ligand **1**, b) product tentatively assigned as macrocycle **3**, c) product tentatively assigned as knot **2** d) expansion of the region between 5.12 and 5.02 ppm of the spectrum of knot **2** showing a propargylic methylene resonance that appears as an AB quartet. The lettering corresponds to that shown in Scheme 5.1.

The material that eluted after 12.6 minutes (Figure 5.2) was attributed as macrocycle **3**, isolated in a yield of 10%. Comparison of the ^{1}H NMR spectra of macrocycle **3** and its acyclic precursor **1** (Figure 5.3b and 5.3a respectively) shows large downfield shifts of the alkyne proton and methylene protons vicinal to the azide (H_s and $H_{s'}$) indicative of triazole formation. The remainder of the proton resonances display only minor differences, this suggests that the environment surrounding these protons has been relatively unaffected by the cycloaddition reaction and is therefore consistent with the formation of a large macrocycle. In sharp contrast, the ^{1}H NMR spectrum of the product isolated in 24% yield after an elution time of 16.5 minutes displays large differences in comparison with ligand **1** and macrocycle **3**. We have assigned this product as the target trefoil knot **2** as the chemical shifts of protons H_s and $H_{s'}$ indicate triazole formation and many of the resonances in the aromatic region are split into two inequivalent sets of signals and are shifted in comparison with macrocycle **3**.

In addition, two of the propargylic methylene resonances of **2** experience a large downfield shift in comparison with the unknotted macrocyclic analogue **3** from 4.6 ppm to 5.3 and 5.1 ppm. We surmise that these protons spend a significant amount of time face-on to an aromatic ring in the lowest energy conformation of the knot and so experience a higher effective magnetic field due to the ring current. Notably, the methylene resonance at 5.1 ppm appears as an AB quartet (Figure 5.3d), implying that the protons are diastereotopic due to the topologically chiral nature of trefoil **2**. The increase in the overall number of discrete resonances observed may be as a result of the loss of the pseudosymmetry of many of the protons of precursor **1** upon formation of the conformationally contorted knot architecture.

If we have indeed synthesized and isolated trefoil **2** as mass spectrometric and ^{1}H NMR evidence seems to suggest, an interesting characteristic of this structure would be the relatively small number of atoms in its framework. The theoretical lower size limit of a trefoil knot composed of a polyethylene backbone has been estimated to be between 45–50 backbone atoms based on molecular modeling[6] whereas Sauvage's 86 atom backbone trefoil reported in 1990 remains the tightest metal-free knot synthesized to date.[7d] Hunter and co-workers recently reported the elegant synthesis of a metal-knot complex with a 77 atom backbone[11d] however in this case the metal center proved to be resistant to demetallation—presumably because the tightly knotted structure lacked the flexibility required to undergo the necessary molecular reorganization. Trefoil **2** reported here comprises just 75 atoms in its backbone, making this the world's smallest knot. The fact that **2** can be demetallated successfully despite its highly compact nature implies that either a sufficient degree of flexibility remains around the metal binding sites to allow the EDTA access to the Cu^{I} centers or that once the knot has formed it is a poor ligand for the Cu^{I} due to its conformational restraints.

In order to obtain unambiguous proof of the topology we have assigned to **2** we hope to be able to obtain a single crystal suitable for analysis by X-ray diffraction. We initially set out to grow crystals of the bimetallic complex **2**.$(CuPF_6)_2$, reasoning that

the metal centers would reduce the degree of conformational freedom of the knot and allow application of the Patterson method during structure refinement. Unfortunately, an amorphous film was formed under all the crystallization conditions trialed. Surprisingly we have had considerably more success growing crystals from a sample of the metal-free trefoil **2**, despite the prospect of conformational flexibility. Slow solvent evaporation from a chloroform–nitromethane solution of **2** afforded crystals of approximately 30 μm length in each dimension. Unfortunately, these crystals induced only very weak diffraction of an incident X-ray beam, failing to provide suitable data to allow the structure to be determined. We are currently trying to grow larger crystals of **2** in order to successfully obtain a solid state structure, should we be able to do so this would be the first crystal structure of a knot in which the template interaction has been removed.

5.3 Conclusions and Outlook

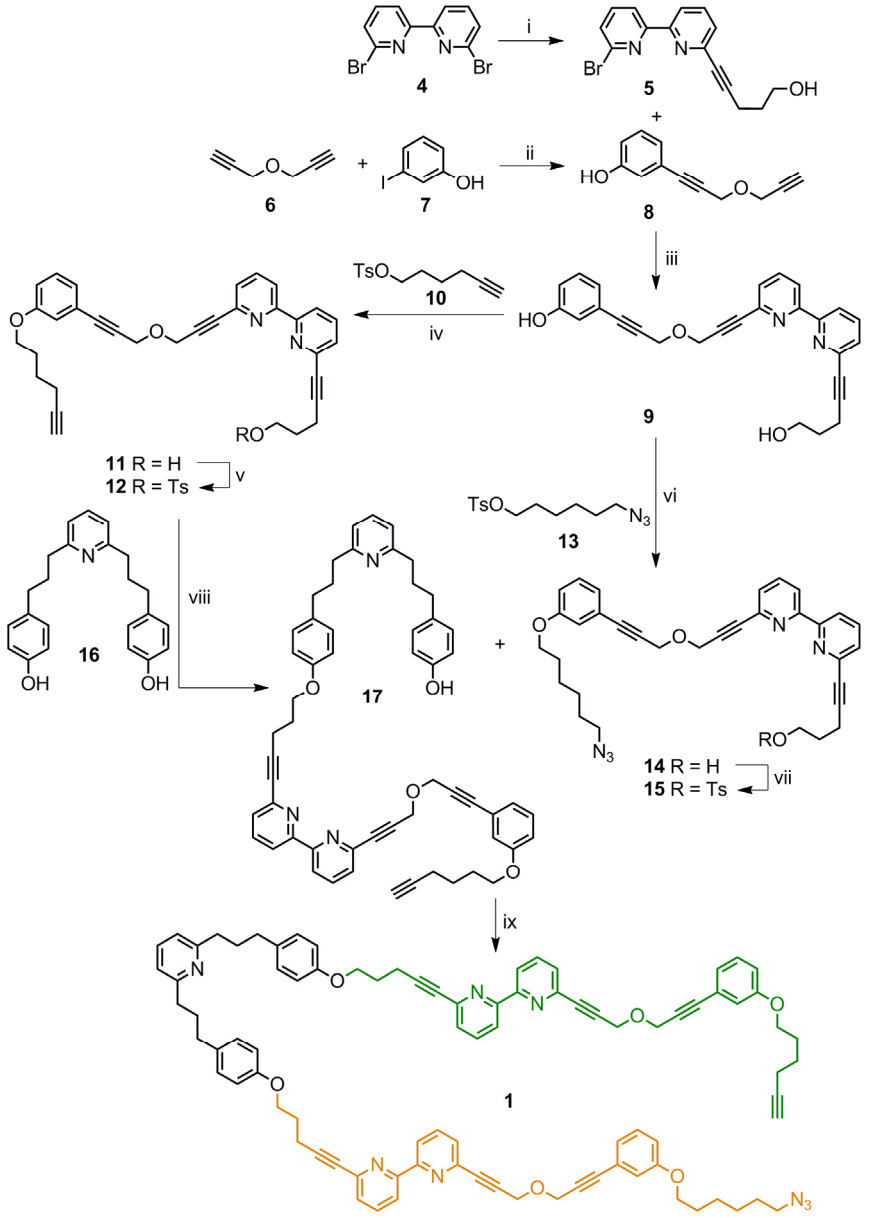
We have successfully synthesized knot precursor **1** and optimized conditions for the AMT CuAAC knot forming reaction to generate products we have tentatively assigned as knot **2** and macrocycle **3**. Our assignments of these products are currently based on mass spectrometric and ^{1}H NMR evidence although we hope to be able to obtain unambiguous proof by analysis of a single crystal of **2** by X-ray diffraction. This proof would confirm the synthesis of the world's smallest knot and would be the first occasion that a template-free molecular knot has been visualized in the solid state.

5.4 Experimental Details

6,6'-Dibromo-2,2'-bipyridine **4**,[16] 2,6-bis(3-(4-hydroxyphenyl)-propyl)-pyridine **14**,[13e] toluene-4-sulfonic acid hex-5-ynyl ester **10**[17] and toluene-4-sulfonic acid 6-azido-hexyl ester **13**[13i] were prepared following literature procedures.

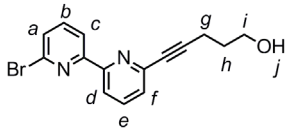
5.4.1 Synthesis of Knot Precursor 1

Scheme 5.2. Synthesis of knot precursor **1** from 6,6'-dibromo-2,2'-bipyridine **4**.



Reagents and conditions: (i) $Pd(dppf)Cl_2$, CuI, Et_3N, toluene, Δ, 18 h, 52%; (ii) $Pd(PPh_3)_4$, CuI, Et_3N, THF, microwave 150 W, 65 °C, 20 min, 98%; (iii) $Pd(dppf)Cl_2$, CuI, Et_3N, MeOH, microwave 150 W, 65 °C, 20 min, 38%; (iv) Cs_2CO_3, DMF, 60 °C, 3 h, 53%; (v) TsCl, Et_3N, CH_2Cl_2, 0 ºC→rt, 18 h, 81%; (vi) Cs_2CO_3, DMF, 60 °C, 3 h, 65%; (vii) TsCl, Et_3N, CH_2Cl_2, 0 ºC→rt, 18 h, 92%; (viii) Cs_2CO_3, DMF, 60 °C, 3 h, 54%; (ix) Cs_2CO_3, DMF, 60 °C, 3 h, 64%.

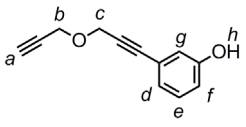
5-(6'-Bromo-[2,2']bipyridinyl-6-yl)-pent-4-yn-1-ol



5

6,6'-Dibromo-2,2'-bipyridine **4**[1] (11.1 g, 35 mmol) was dissolved in toluene (300 mL), Et_3N (200 mL) and MeOH (60 mL) and the resulting solution was degassed. $Pd(dppf)Cl_2$ (1.44 g, 1.75 mmol), CuI (672 mg, 3.5 mmol) and 4-pentyn-1-ol (3.6 mL, 39 mmol) were added and the reaction mixture heated at reflux for 18 h. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH_2Cl_2 with 5% acetone, 2. CH_2Cl_2 with 10% acetone) to give **5** as a cream colored solid (5.9 g, 52%). M.p 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (dd, 1H, *J* = 7.7, 0.8, H_c), 8.33 (dd, 1H, *J* = 8.0, 0.9, H_d), 7.76 (t, 1H, *J* = 7.8, H_b), 7.66 (t, 1H, *J* = 7.8, H_e), 7.49 (dd, 1H, *J* = 7.8, 0.8, H_a), 7.42 (dd, 1H *J* = 7.7, 1.0, H_f), 3.86 (t, 2H, *J* = 6.1, H_i), 2.62 (t, 2H, *J* = 7.0, H_g), 1.97 – 1.88 (m, 2H, H_h); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 154.6, 143.1, 141.4, 139.1, 137.1, 128.1, 127.4, 120.3, 120.1, 90.0, 80.8, 61.6, 31.0, 16.0; LRAPCI-MS: *m/z* = 317 $[M+H]^+$; HRESI-MS: *m/z* = 317.0285 $[M+H]^+$ (calc. for $C_{15}H_{14}ON_2{}^{79}Br$ 317.0284).

3-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenol

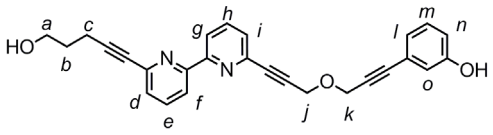


8

3-Iodophenol **7** (3.0 g, 13.6 mmol) was dissolved in THF (30 mL) and Et_3N (15 mL) and the resulting solution was degassed. $Pd(PPh_3)_4$ (700 mg, 0.60 mmol), CuI (228 mg, 1.2 mmol) and propargyl ether **6** (5 mL, 48.5 mmol) were added and the reaction

mixture heated at 65 °C using microwave irradiation (150W maximum) for 20 min. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH_2Cl_2-petrol 3:1, 2. CH_2Cl_2) to give **8** as an orange oil (2.5 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, 1H, *J* = 7.9, H_e), 7.03 (d, 1H, *J* = 7.6, H_d), 6.92 (dd, 1H, *J* = 2.2, 1.5, H_g), 6.82 (ddd, 1H, *J* = 8.1, 2.6, 0.6, H_f), 4.94 (s, 1H, H_h), 4.48 (s, 2H, H_c), 4.32 (d, 2H, *J* = 2.4, H_b), 2.48 (t, 1H *J* = 2.4 Hz, H_a; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 129.6, 124.4, 123.5, 118.3, 116.0, 86.4, 84.0, 78.8, 75.0, 57.2, 56.5; LRAPCI-MS: *m/z* = 187 $[M+H]^+$; HRESI-MS: *m/z* = 317.0285 $[M+H]^+$ (calc. for $C_{15}H_{14}ON_2{}^{79}Br$ 317.0284).

3-(3-{3-[6'-(5-Hydroxy-pent-1-ynyl)-[2,2']bipyridinyl-6-yl]-prop-2-ynyloxy}-prop-1-ynyl)-phenol

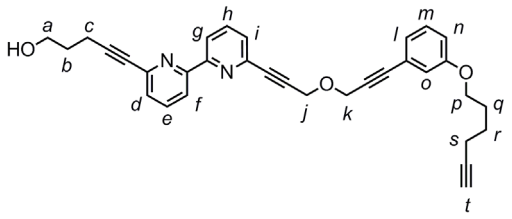


9

5 (2.2 g, 6.93 mmol) was dissolved in MeOH (60 mL) and Et_3N (30 mL) and the resulting solution was degassed. $Pd(dppf)Cl_2$ (283 mg, 346 μmol), CuI (132 mg, 692 μmol) and **8** (1.51 g, 8.12 mmol) were added and the reaction mixture heated at 65 °C using microwave irradiation (150W maximum) for 20 min. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2 with 5→20% acetone) to give **9** as an orange oil (1.12 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, 1H, *J* = 8.0, 0.9, H_g), 8.33 (dd, 1H, *J* = 8.0, 0.9 Hz, H_f), 7.80 – 7.72 (m, 2H, H_e + H_h), 7.48 (dd, 1H, *J* = 7.7, 0.9, H_i), 7.41 (dd, 1H, *J* = 7.7, 0.8, H_d), 7.17 (t, 1H, *J* = 7.9, H_m), 7.03 (d, 1H, *J* = 7.7, H_l), 6.92 (s, 1H, H_o), 6.82 (dd, 1H, *J* = 8.1, 1.9, H_n), 4.59 (s, 2H, H_j or H_k), 4.57 (s, 2H, H_j or H_k), 3.86 (t, 2H, *J* = 6.1, H_a), 2.61 (t, 2H, *J* = 7.0, H_c), 1.96 – 1.87 (m, 2H, H_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 155.5, 155.4, 143.0, 141.9, 141.7, 137.1, 132.0, 129.5, 128.4, 127.5, 127.2, 124.3, 121.1, 120.4,

118.4, 116.1, 90.0, 86.2, 84.3, 84.1, 80.9, 61.6, 57.7, 57.3, 30.9, 16.0; LRAPCI-MS: *m/z* = 423 $[M+H]^+$; HRESI-MS: *m/z* = 423.1700 $[M+H]^+$ (calc. for $C_{27}H_{23}O_3N_2$ 423.1703).

5-(6'-{3-[3-(3-Hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-yn-1-ol

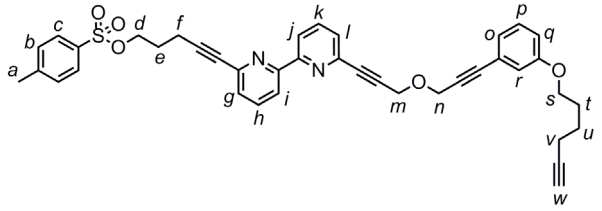


11

Toluene-4-sulfonic acid hex-5-ynyl ester **10**[3] (735 mg, 2.91 mmol) was added to a solution of **9** (820 mg, 1.94 mmol) and Cs_2CO_3 (1.26 g, 3.88 mmol) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc (40 mL) and H_2O (40 mL). The phases were separated and the organic phase was further extracted with H_2O (2 x 40 mL) and brine (2 x 40 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: CH_2Cl_2 with 2→10% acetone) to give **11** as an orange oil (518 mg, 53%).[1]H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, *J* = 7.1, H_g), 8.37 (d, 1H, *J* = 7.1, H_f), 7.81 – 7.72 (m, 2H, H_e + H_h), 7.51 – 7.46 (m, 1H, H_i), 7.44 – 7.39 (m, 1H, H_d), 7.23 – 7.17 (m, 1H, H_m), 7.05 (d, 1H, *J* = 7.6, H_l), 6.99 (d, 1H, *J* = 2.5, H_o), 6.87 (dd, 1H, *J* = 7.9, 2.1, H_n), 4.61 (s, 2H, H_j or H_k), 4.58 (s, 2H, H_j or H_k), 3.97 (t, 2H, *J* = 6.3 Hz, H_p), 3.86 (t, 2H, *J* = 6.1, H_a), 2.62 (t, 2H, *J* = 7.0, H_c), 2.27 (td, 2H, J_d = 7.0, J_t = 2.6, H_s), 1.97 (t, 1H, *J* = 2.6, H_t), 1.96 – 1.85 (m, 4H, H_b + H_q), 1.76 – 1.66 (m, 2H, H_r); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 155.8, 155.4, 142.9, 141.8, 137.0, 137.0, 129.3, 127.5, 127.2, 124.2, 123.2, 121.0, 120.3, 117.1, 115.7, 89.9, 86.9, 86.1, 84.2, 83.9, 83.9, 80.9, 68.6, 67.2, 61.6, 57.6, 57.2, 30.9, 28.1, 24.9, 18.0, 16.0; LRAPCI-

MS: *m/z* = 503 $[M+H]^+$; HRESI-MS: *m/z* = 503.2330 $[M+H]^+$ (calc. for $C_{33}H_{31}O_3N_2$ 503.2329).

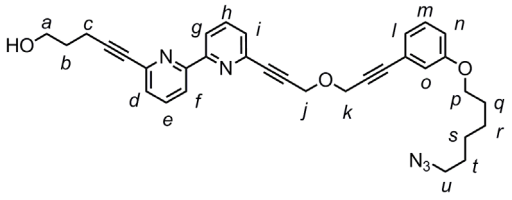
Toluene-4-sulfonic acid 5-(6'-{3-[3-(3-hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-ynyl ester



12

To a solution of **11** (345 mg, 686 µmol) and Et_3N (190 µL, 1.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (144 mg, 755 µmol) and the reaction allowed to stir at rt for 18 h. The crude reaction mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (gradient elution: 1. 3:1 petrol-CH_2Cl_2, 2. 3:1:1 petrol-CH_2Cl_2-EtOAc) to give **12** as a yellow oil (366 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.33 (m, 2H, H_i + H_j), 7.80 (d, 2H, *J* = 8.3, H_c), 7.78 – 7.70 (m, 2H, H_h + H_k), 7.47 (d, 1H, *J* = 7.6, H_l), 7.31 (d, 1H, *J* = 7.6, H_g), 7.28 (d, 2H, *J* = 8.1, H_b), 7.19 (t, 1H, *J* = 7.9, H_p), 7.03 (d, 1H, *J* = 7.6, H_o), 6.97 (d, 1H, *J* = 2.1, H_r), 6.86 (dd, 1H, *J* = 8.3, 2.4, H_q), 4.59 (s, 2H, H_m or H_n), 4.57 (s, 2H, H_m or H_n), 4.21 (t, 2H, *J* = 6.0, H_d), 3.95 (t, 2H, *J* = 6.3, H_s), 2.54 (t, 2H, *J* = 6.9, H_f), 2.34 (s, 3H, H_a), 2.25 (td, 2H, J_d = 7.0, J_t = 2.6, H_v), 2.02 – 1.93 (m, 3H, H_e + H_w), 1.88 (m, 2H, H_t), 1.76 – 1.64 (m, 2H, H_u); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 155.7, 155.4, 144.7, 142.6, 141.8, 137.0, 136.9, 132.7, 129.7, 129.3, 127.8, 127.4, 127.2, 124.1, 123.2, 120.9, 120.3, 117.0, 115.6, 87.9, 86.8, 86.1, 84.2, 83.9, 83.8, 81.4, 68.7, 68.6, 67.2, 57.6, 57.1, 28.0, 27.4, 24.8, 21.5, 18.0, 15.6; LRAPCI-MS: *m/z* = 657 $[M+H]^+$; HRESI-MS: *m/z* = 657.2419 $[M+H]^+$ (calc. for $C_{40}H_{37}O_5N_2S$ 657.2418).

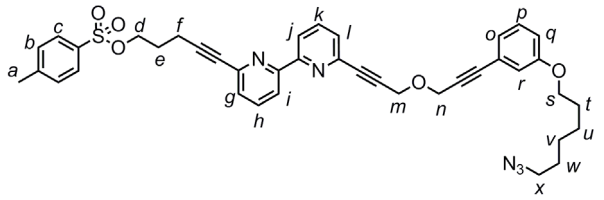
5-[6'-(3-{3-[3-(6-Azido-hexyloxy)-phenyl]-prop-2-ynyloxy}-prop-1-ynyl)-[2,2']bipyridinyl-6-yl]-pent-4-yn-1-ol



14

Toluene-4-sulfonic acid 6-azido-hexyl ester **13**[4] (535 mg, 1.8 mmol) was added to a solution of **9** (507 mg, 1.2 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc (40 mL) and H_2O (40 mL). The phases were separated and the organic phase was further extracted with H_2O (2 x 40 mL) and brine (2 x 40 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH_2Cl_2 with 2% acetone, 2. CH_2Cl_2 with 5% acetone) to give **14** as an orange oil (430 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 8.0, H_g), 8.37 (d, 1H, J = 7.9, H_f), 7.81 – 7.72 (m, 2H, H_e + H_h), 7.48 (d, 1H, J = 7.6, H_i), 7.41 (d, 1H, J = 7.7, H_d), 7.23 – 7.18 (m, 1H, H_m), 7.05 (dt, 1H, J = 7.6, 1.1, H_l), 6.98 (dd, 1H, J = 2.4, 1.4, H_o), 6.87 (ddd, 1H, J = 8.3, 2.6, 0.8, H_n), 4.60 (s, 2H, H_j or H_k), 4.58 (s, 2H, H_j or H_k), 3.94 (t, 2H, J = 6.4 Hz, H_p), 3.85 (t, 2H, J = 6.1, H_a), 3.28 (t, 2H, J = 6.9, H_u), 2.62 (t, 2H, J = 7.0, H_c), 1.93 (p, 2H, J = 6.6, H_b), 1.83 – 1.73 (m, 2H, H_q), 1.68 – 1.58 (m, 2H, H_t), 1.54 – 1.39 (m, 4H, H_r + H_s); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 155.8, 155.5, 142.9, 141.9, 137.0, 137.0, 129.3, 127.5, 127.2, 124.2, 123.3, 121.1, 120.3, 117.1, 115.7, 89.9, 86.9, 86.2, 84.2, 83.9, 80.9, 67.7, 61.7, 57.6, 57.2, 51.3, 31.0, 29.0, 28.7, 26.4, 25.6, 16.0; LRAPCI-MS: *m/z* = 548 $[M+H]^+$; HRESI-MS: *m/z* = 548.2675 $[M+H]^+$ (calc. for $C_{33}H_{34}O_3N_5$ 548.2656).

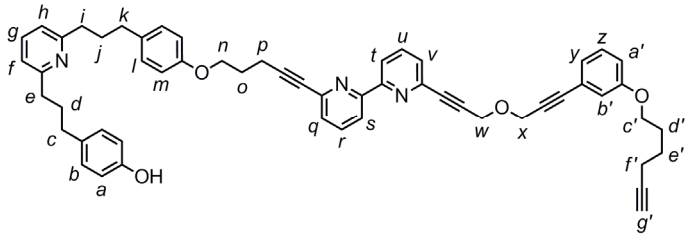
Toluene-4-sulfonic acid 5-[6'-(3-{3-[3-(6-azido-hexyloxy)-phenyl]-prop-2-ynyloxy}-prop-1-ynyl)-[2,2']bipyridinyl-6-yl]-pent-4-ynyl ester



15

To a solution of **14** (244 mg, 450 µmol) and Et_3N (130 µL, 0.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (93 mg, 490 µmol) and the reaction allowed to stir at rt for 18 h. The crude reaction mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2 with 2% acetone) to give **15** as an orange oil (288 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.34 (m, 2H, H_i + H_j), 7.81 (d, 2H, J = 8.3, H_c), 7.78 (t, 1H, J = 7.0, H_k), 7.74 (t, 1H, J = 7.0, H_h), 7.48 (dd, 1H, J = 7.7, 1.0, H_l), 7.33 (dd, 1H, J = 7.7, 1.0, H_g), 7.30 (d, 2H, J = 7.9, H_b), 7.23 – 7.18 (m, 1H_p), 7.05 (dt, 1H, J_d = 7.6, J_t = 1.1, H_o), 6.98 (dd, 1H, J = 2.4, 1.4, H_r), 6.87 (ddd, 1H, J = 8.3, 2.6, 0.9, H_q), 4.61 (s, 2H, H_m or H_n), 4.58 (s, 2H, H_m or H_n), 4.23 (t, 2H, J = 6.0, H_d), 3.94 (t, 2H, J = 6.4, H_s), 3.28 (t, 2H, J = 6.9, H_x), 2.55 (t, 2H, J = 6.9, H_f), 2.36 (s, 3H, H_a), 2.04 – 1.96 (m, 2H, H_e), 1.82 – 1.74 (m, 2H, H_t), 1.68 – 1.59 (m, 2H, H_w), 1.54 – 1.39 (m, 4H, H_u + H_v); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 155.7, 155.4, 144.7, 142.6, 141.9, 137.1, 137.0, 132.8, 129.8, 129.3, 127.9, 127.5, 127.3, 124.1, 123.3, 121.0, 120.5, 117.1, 115.7, 88.2, 86.9, 86.1, 84.3, 83.9, 81.4, 68.8, 67.7, 57.7, 57.2, 51.3, 29.0, 28.7, 27.5, 26.4, 25.6, 21.5, 15.7; LRAPCI-MS: *m/z* = 702 $[M+H]^+$; HRESI-MS: *m/z* = 702.2734 $[M+H]^+$ (calc. for $C_{40}H_{40}O_5N_5S$ 702.2745).

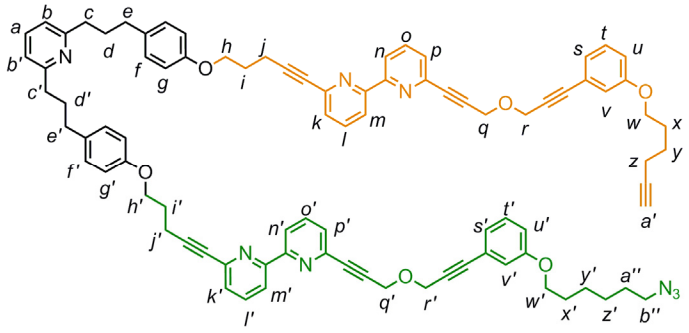
4-{3-[6-(3-{4-[5-(6'-{3-[3-(4-Hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-ynyloxy]-phenyl}-propyl)-pyridin-2-yl]-propyl}-phenol



17

12 (152 mg, 231 μmol) was added to a solution of 2,6-bis(3-(4-hydroxyphenyl)-propyl)-pyridine **16**[2] (241 mg, 694 μmol) and Cs_2CO_3 (226 mg, 694 μmol) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 2 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc (40 mL) and H_2O (40 mL). The phases were separated and the organic phase was further extracted with H_2O (2 x 40 mL) and brine (2 x 40 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH_2Cl_2 with 2% acetone, 2. CH_2Cl_2 with 4% acetone) to give **17** as a yellow oil (103 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, 1H, J = 8.0, 0.9, H_t), 8.35 (dd, 1H, J = 8.0, 0.9, H_s), 7.78 – 7.70 (m, 2H, H_r + H_u), 7.50 (t, 1H, J = 7.7, H_g), 7.47 (dd, 1H, J = 7.7, 0.9, H_v), 7.39 (dd, 1H, J = 7.7, 0.8, H_q), 7.21 (t, 1H, J = 8.0, H_z), 7.07 – 7.00 (m, 3H, H_l + H_y), 7.00 – 6.92 (m, 5H, H_f + H_h + H_m + $H_{b'}$), 6.87 (dd, 1H, J = 8.3, 1.9, $H_{a'}$), 6.79 (d, 2H, J = 8.6, H_b), 6.67 (d, 2H, J = 8.5, H_a), 4.60 (s, 2H, H_w or H_x), 4.57 (s, 2H, H_w or H_x), 4.08 (t, 2H, J = 6.0, H_n), 3.96 (t, 2H, J = 6.3, $H_{c'}$), 2.83 – 2.74 (m, 4H, H_e + H_i), 2.68 (t, 2H, J = 7.0, H_p), 2.64 – 2.53 (m, 4H, H_c + H_k), 2.27 (td, 2H J_t = 7.0, J_d = 2.6, $H_{f'}$), 2.14 – 2.06 (m, 2H, H_o), 2.04 – 1.85 (m, 6H, H_d + H_j + $H_{d'}$), 1.70 (m, 2H, $H_{e'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 161.3, 158.6, 156.8, 155.8, 155.4, 154.3, 143.0, 141.8, 137.1, 137.0, 136.8, 134.3, 133.2, 129.3, 129.3, 127.5, 127.3, 127.2, 124.2, 123.2, 121.1, 121.1, 120.4, 120.0, 117.1, 115.7, 115.1, 114.2, 89.9, 86.9, 86.1, 84.3, 84.0, 83.9, 80.8, 68.6, 67.2,

66.2, 61.6, 57.6, 57.2, 37.5, 34.6, 34.5, 32.0, 31.8, 29.6, 28.1, 24.9, 18.0, 16.2; LRAPCI-MS: *m/z* = 823 $[M+H]^+$; HRESI-MS: *m/z* = 832.4095 $[M+H]^+$ (calc. for $C_{56}H_{54}O_4N_3$ 832.4109).

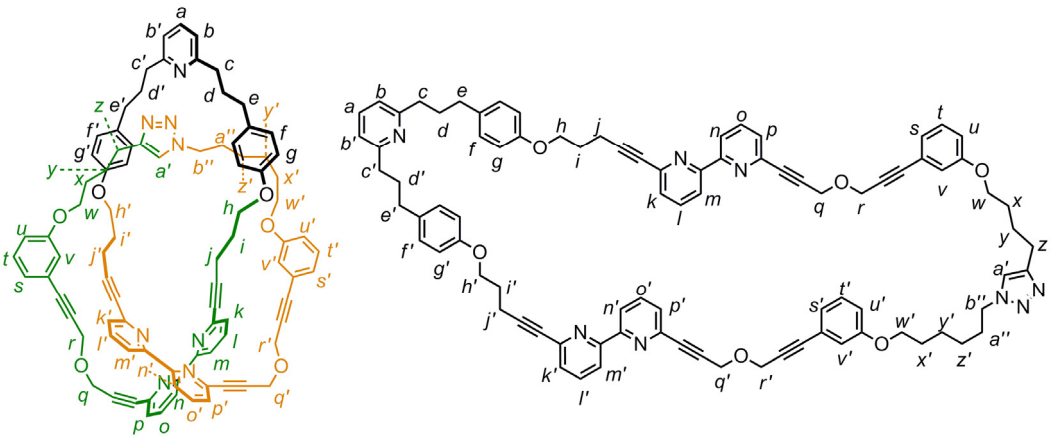


1

15 (288 mg, 410 µmol) was added to a solution of **17** (180 mg, 216 µmol) and Cs_2CO_3 (141 mg, 432 µmol) in DMF (2.5 mL) and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc (10 mL) and H_2O (10 mL). The phases were separated and the organic phase was further extracted with H_2O (2 x 10 mL) and brine (2 x 10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: CH_2Cl_2 with 1→4% EtOAc) to give **1** as a yellow oil (187 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, 2H, *J* = 8.0, $H_n + H_{n'}$), 8.36 (d, 2H, *J* = 7.9, $H_m + H_{m'}$), 7.78 – 7.69 (m, 4H, $H_l + H_o + H_{l'} + H_{o'}$), 7.50 – 7.44 (m, 3H, $H_a + H_p + H_{p'}$), 7.39 (d, 2H, *J* = 7.6, $H_k + H_{k'}$), 7.20 (t, 2H, *J* = 8.0, $H_t + H_{t'}$), 7.09 (t, 4H, *J* = 7.1, $H_f + H_{f'}$), 7.05 (d, 2H, *J* = 7.6, $H_s + H_{s'}$), 6.98 (s, 2H, $H_v + H_{v'}$), 6.93 (d, 2H, *J* = 7.7, $H_b + H_{b'}$), 6.90 – 6.81 (m, 6H, $H_g + H_u + H_{g'} + H_{u'}$), 4.60 (s, 4H, H_q or $H_r + H_{q'}$ or $H_{r'}$), 4.57 (s, 4H, H_q or $H_r + H_{q'}$ or $H_{r'}$), 4.10 (t,, 4H, *J* = 6.0, $H_h + H_{h'}$), 3.98 – 3.90 (m, 4H, $H_w + H_{w'}$), 3.27 (t, 2H, *J* = 6.9, $H_{b''}$), 2.82 – 2.75 (m, 4H, $H_c + H_{c'}$), 2.69 (t, 4H, *J* = 7.0, $H_j + H_{j'}$), 2.65 – 2.58 (m, 4H, $H_e + H_{e'}$), 2.27 (td, 2H, J_t = 7.0, J_d = 2.6, H_z), 2.17 – 2.08 (m, 4H, $H_i + H_{i'}$), 2.03 – 1.94 (m, 5H, $H_d + H_{a'} + H_{d'}$), 1.94 – 1.83 (m, 2H, H_x), 1.82 – 1.73 (m, 2H, $H_{x'}$), 1.73 – 1.56 (m, 4H, $H_y + H_{a''}$), 1.53 – 1.35 (m, 4H, $H_{y'} + H_{z'}$); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 161.3 (2xC), 158.6, 158.6, 156.9 (2xC), 155.8 (2xC), 155.4 (2xC), 142.9 (2xC), 141.8 (2xC), 137.0 (2xC), 136.9 (2xC), 136.4 (2xC), 134.4 (2xC), 129.3 (2xC), 127.5, 127.4 (2xC), 127.3 (2xC), 124.1, 124.1, 123.2 (2xC), 121.0 (2xC), 120.2 (2xC), 119.7 (2xC), 117.0 (2xC), 115.7 (2xC), 114.3 (2xC), 89.7 (2xC), 86.9, 86.9, 86.1 (2xC), 84.1 (2xC), 83.9 (2xC), 83.9, 80.9 (2xC), 68.6 (2xC), 67.6, 67.2, 66.2, 57.6 (2xC), 57.2 (2xC), 51.2, 37.9 (2xC), 34.6 (2xC), 31.9 (2xC), 29.5, 28.9, 28.7, 28.1, 28.0, 26.4, 25.5, 24.9, 18.0, 16.2 (2xC); LRAPCI-MS: *m/z* = 1362 $[M+H]^+$; HRESI-MS: *m/z* = 1361.6613 $[M+H]^+$ (calc. for $C_{88}H_{89}O_{10}N_4$ 1361.6573).

5.4.2 Synthesis of Knot 2 and Macrocycle 3



Trefoil knot **2** and macrocycle **3**

A solution of $[(CH_3CN)_4Cu]PF_6$ (14.7 mg, 39.4 µmol) in CH_3NO_2 (2.5 mL) was added to a solution of **1** (35.8 mg, 26.3 µmol) in $CHCl_3$ (14 mL) and CH_3NO_2 (1.0 mL) and the reaction mixture was heated to 60 °C for 96 h. The reaction mixture was allowed to cool to rt, diluted with CH_2Cl_2 (30 mL) then a 17.5% aqueous solution of NH_3 saturated with Na_2EDTA (30 mL) was added and stirred vigorously for 30 min. The phases were separated and the organic phase was further extracted with a 17.5% aqueous solution of NH_3 saturated with Na_2EDTA (30 mL), H_2O (30 mL) and brine (30 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by size exclusion chromatography (CH_2Cl_2 mobile phase) followed by preparative HPLC (reverse phase column, gradient elution: 1. MeOH

with 5→0% H_2O, 2. MeOH with 0→10% CH_2Cl_2) to give trefoil knot **2** as a colorless film (8.6 mg, 24%) and macrocycle **3** as a yellow film (3.5 mg, 10%).

Trefoil knot **2**

^{1}H NMR (500 MHz, $CDCl_3$) partially assigned δ 8.56 (dd, *J* = 7.9, 0.7, 1H), 8.46 (d, *J* = 8.9, 1H), 8.37 (d, *J* = 7.9, 1H), 8.31 (dd, *J* = 7.9, 0.9, 1H), 8.13 (d, *J* = 8.9, 1H), 7.98 (s, 1H), 7.79 (t, *J* = 7.8, 1H), 7.75 – 7.66 (m, 2H), 7.42 (dt, *J* = 11.6, 10.5, 4H), 7.35 (d, *J* = 7.5, 1H), 7.27 (s, 1H, $H_{a'}$), 7.21 – 7.14 (m, 2H, H_t + $H_{t'}$), 7.07 (dd, *J* = 8.6, 2.2, 5H), 7.02 (d, *J* = 7.6, 1H), 6.98 (dd, *J* = 8.3, 1.9, 1H), 6.95 (dd, *J* = 2.3, 1.4, 1H), 6.92 (d, *J* = 7.6, 2H), 6.87 – 6.85 (m, 1H), 6.85 – 6.77 (m, 6H), 5.33 (s, 2H, H_q or H_r or $H_{q'}$ or $H_{r'}$), 5.07 (AB quartet, 2H, H_q or H_r or $H_{q'}$ or $H_{r'}$), 4.59 (s, 2H, H, H_q or H_r or $H_{q'}$ or $H_{r'}$), 4.56 (s, 2H, H_q or H_r or $H_{q'}$ or $H_{r'}$), 4.30 (t, *J* = 7.1, 2H, $H_{s'}$), 4.14 – 4.06 (m, 4H, H_h + $H_{h'}$), 4.00 (t, *J* = 4.9, 2H), 3.88 (t, *J* = 6.3, 2H), 2.79 (br, 4H), 2.72 – 2.65 (m, 6H), 2.14 – 2.06 (m, 6H), 1.93 – 1.84 (m, 6H), 1.76 – 1.69 (m, 2H), 1.50 – 1.41 (m, 2H), 1.39 – 1.26 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (2xC), 158.6 (2xC), 156.4 (2xC), 155.9 (2xC), 155.5, 155.1, 148.2, 147.8, 143.1, 141.9, 141.7, 138.2, 137.6, 137.1, 137.0, 134.7 (2xC), 132.4 (2xC), 129.9 (2xC), 129.4 (2xC), 127.5, 127.4, 127.3, 126.6, 124.2, 123.4, 121.7, 121.1, 120.6, 120.6, 120.5, 120.3, 118.9, 117.2, 115.8, 115.5, 114.5, 114.5, 114.4, 114.2, 89.7, 89.6, 87.0, 86.3 (2xC), 84.3, 84.0, 81.2, 81.1, 73.3, 72.7, 67.7, 67.6, 66.3, 66.2, 65.0, 57.7, 57.3, 53.4, 50.9, 50.0, 31.9, 30.2, 29.7, 29.7, 29.4, 28.8, 28.8, 28.2, 27.9, 26.1, 26.0, 25.4, 25.4, 22.7, 16.3, 16.1, 14.1; LRESI-MS: *m/z* = 1362 $[M+H]^+$; HRESI-MS: *m/z* = 1361.6601 $[M+H]^+$ (calc. for calc. for $C_{88}H_{85}N_8O_6$ 1361.6597).

Macrocycle **3**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.9, 2H, H_n + $H_{n'}$), 8.33 (d, *J* = 7.8, 2H, H_m + $H_{m'}$), 7.77 – 7.66 (m, 4H, H_l + H_o + $H_{l'}$ + $H_{o'}$), 7.50 – 7.40 (m, 3H, H_a + H_p + $H_{p'}$), 7.37 (d, *J* = 7.0, 2H, H_k + $H_{k'}$), 7.25 (s, 1H, H_a), 7.21 – 7.16 (m, 2H, H_t + $H_{t'}$), 7.08 (d, *J* = 8.6, 4H, H_f + $H_{f'}$), 7.03 (d, *J* = 7.6, 2H, H_s + $H_{s'}$), 6.96 (dd, *J* = 3.8, 2.6, 2H, H_v + $H_{v'}$), 6.93 (d, *J* = 7.6, 2H, H_b + $H_{b'}$), 6.88 – 6.80 (m, 6H, H_g + H_u +$H_{g'}$ +

$H_{u'}$), 4.59 (s, 4H, H_q or H_r + $H_{q'}$ or $H_{r'}$), 4.57 (s, 4H, H_q or H_r + $H_{q'}$ or $H_{r'}$), 4.30 (t, J = 7.1, 2H, $H_{b''}$), 4.11 (t, J = 6.0, 4H, H_h + $H_{h'}$), 3.98 – 3.87 (m, 4H, H_w + $H_{w'}$), 2.82 – 2.72 (m, 6H, H_c + H_z + $H_{c'}$), 2.68 (t, J = 6.9, 4H, H_j + $H_{j'}$), 2.64 – 2.55 (m, 4H, H_e + $H_{e'}$), 2.15 – 2.05 (m, 4H, H_i + $H_{i'}$), 2.06 – 1.94 (m, 4H, H_d + $H_{d'}$), 1.94 – 1.85 (m, 2H, H_x), 1.85 – 1.78 (m, 4H, $H_{x'}$ + $H_{a''}$), 1.78 – 1.69 (m, 2H, H_y), 1.52 – 1.31 (m, 4H, $H_{x'}$ + $H_{y'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3 (2xC), 158.6 (2xC), 156.9 (2xC), 155.9 (2xC), 155.5 (2xC), 147.8, 143.00 (2xC), 141.9 (2xC), 137.5 (2xC), 137.1 (2xC), 137.0 (2xC), 134.8 (2xC), 129.4 (2xC), 129.3 (2xC), 127.5, 127.3, 124.2, 124.2, 123.3, 123.3, 121.1 (2xC), 120.6 (2xC), 120.4 (2xC), 117.3 (2xC), 117.2 (2xC), 115.7, 115.7, 114.4 (2xC), 89.7 (2xC), 87.0, 86.2 (2xC), 84.3 (2xC), 84.0 (2xC), 81.0 (2xC), 67.6 (2xC), 67.5, 66.3, 65.0, 57.7 (2xC), 57.2 (2xC), 50.0, 31.9 (2xC), 30.0 (2xC), 29.6 (2xC), 28.8, 28.6, 28.0, 26.1, 25.9, 25.4, 25.2, 22.7, 16.1, 14.1 (2xC); LRESI-MS: *m/z* = 1362 $[M+H]^+$; HRESI-MS: *m/z* = 1361.6603 $[M+H]^+$ (calc. for calc. for $C_{88}H_{85}N_8O_6$ 1361.6597).

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CHAPT. 6 | SYNTHESIS AND CHARACTERIZATION OF NOVEL AGROCHEMICAL-BASED ROTAXANES

Synopsis

The ability of the macrocyclic component of a rotaxane to alter the physical properties and chemical stability of the encapsulated thread has led to increasing interest in these architectures for potential biological applications. This Chapter describes the design, synthesis and biological assessment of rotaxanes bearing agrochemical motifs.

Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Andrew Plant (*Syngenta*) provided valuable advice and guidance throughout the project; Mike Turnbull (*Syngenta*) evaluated the biological efficacy of compounds **4**–**7** in addition to providing useful advice. The Author also wishes to thank Dr. Stephen Goldup, Dr. Dominik Heckmann and Dr. Bartosz Lewandowski for assistance with retrosynthetic analyses.

6.1 Introduction

6.1.1 Herbicides

Agriculture can be considered as the science of cultivating soil, growing crops and raising livestock. In some parts of the world there is evidence of agriculture up to ten thousand years ago and it is still of enormous importance today.[1] Efficiently growing crops to meet the demands of humankind requires conditions to be artificially improved, providing an environment that encourages crop growth whilst simultaneously excluding pests and weeds. Weeds compete with crops for nutrients, moisture and sunlight so the need for methods of destroying weeds is important and ever-present. In past centuries, the method employed to achieve this goal has been to physically remove weeds. Doing so by hand is labor intensive, even with the growth of industrialization and mechanical means of weed removal, physical weed removal requires a large input of manpower and money. The alternative—often more cost and time effective—method is to use chemicals to control weed growth and this tactic has been used for over a century.

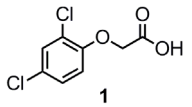
Broadly speaking a herbicide is simply any chemical that destroys or inhibits plant growth. Early herbicides were rather unsophisticated, highly toxic chemicals such as crushed arsenic ores and sulfuric acid. These were used in large doses to destroy all plant life in a given area in preparation for activities such as construction work and laying roads or railway tracks. Such a heavy handed approach is not suitable for agriculture; ideally a herbicide used in agriculture should kill weeds but leave crops unharmed. In the early 1900s a few cases of selective inorganic herbicides emerged, however these had limited use and it is the use of organic small-molecule selective herbicides that has proven to be the most fruitful approach. Selectivity in these organic herbicides can usually be attributed to any of three factors; biochemical differences, physiochemistry or morphology.

Biochemical differences between crops and weeds have been exploited in a few cases. If the crop possesses a defense mechanism against the herbicide that the weed

does not then the herbicide can be applied safely for selective weed control. The morphology of the plants themselves can also contribute to selectivity. Some plants have broad leaves with a large surface area whereas others, such as grasses, have narrow upright leaves. As a result, broad leaved weeds have more tissue exposed to a herbicide applied as a spray and so are more affected. The physiochemistry of the herbicide may play a crucial role; often the aqueous solubility and interactions with the soil determine if the herbicide is absorbed by some plants. An example of this is soil-applied triazine herbicides, such as Metribuzin, which only penetrate up to 5 cm down into the soil because of low aqueous solubility. Consequently deep rooted crops remain unaffected however germinating weed seeds are killed.

6.1.1.1 2,4-Dichlorophenoxyacetic acid

2,4-Dichlorophenoxyacetic acid (2,4-D) **1** is part of the phenoxyacetic acid, or synthetic auxin, family of herbicides and is one of the most widely used herbicides in the world today (Figure 6.1).



1

Figure 6.1. 2,4-Dichlorophenoxyacetic acid **1**.

Phenoxyacetic acids were first studied for herbicidal activity by Kögl in 1934.[2] He investigated structures related to the natural product indole-3-acetic acid, also known as auxin, which was already known to be phytohormone responsible for growth regulation in plants.[3] In 1942, Zimmerman and Hitchcock showed that 2,4-D is more active than auxin and is less rapidly metabolized.[4] It acts as a selective herbicide, killing broad leaf weeds and causing relatively little damage to cereals and grasses. The selectivity is not fully understood although it can partly be attributed to the morphology of the leaves of the plants as discussed above.

6.1.1.2 Fluazifop

Fluazifop **2**, or {2-[4-(5-trifluoromethyl-2-pyridyloxy)-phenoxy]-propionic acid}, is a commercial herbicide marketed under the name Fusilade (Figure 6.2) and often administered as a racemate and as pro-herbicide fluazifop-p-butyl ester **3**.

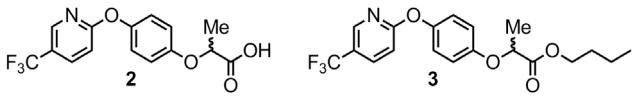


Figure 6.2. Fluazifop **2** and fluazifop-p-butyl ester **3**.

Fluazifop **2** is a member of the aryloxyphenoxypropionate family of herbicides which cause rapid necrosis of the meristematic tissue of sensitive plant species[5] by inhibiting fatty acid synthesis at the level of the acetyl-CoA carboxylase enzyme.[6] It is grass specific; in this case selectivity arises as a result of variations in the biochemical sensitivities of different plant species.

6.1.2 Rotaxanes with Potential Biological Applications

As well as being prototypical design elements for various types of molecular machines, rotaxanes often dramatically change the properties of their components (including solubility,[7] photostability,[8] and membrane transport[9]) and can protect encapsulated regions of threaded substrates from chemical attack and metabolic degradation. For these reasons there has been increasing interest in the rotaxane architecture as a means of encapsulating a substrate for potential biological applications.

Incorporation of squaraine dyes into the thread component of rotaxane architectures has been shown to result in enhanced stability and dye fluorescence as well as different cell localization propensities in comparison with non-encapsulated analogues.[10] Silica 'nano-capsules' have been developed in which the release of substrates from within a silica bead is controlled by the shuttling dynamics of bistable rotaxane 'nano-valves' attached to the bead surface.[11] Recently, a 'propeptide rotaxane' was developed in which the macrocyclic belt shielded a pentapeptide from various peptidases.[12] A carbohydrate 'trigger'—which also formed part of a

stoppering group—could be cleaved selectively by a glycosidase allowing dissociation of the macrocycle and release of the parent peptide.

We aimed to synthesize rotaxanes bearing agrochemical motifs as part of the dumbbell component and to assess these compounds in collaboration with *Syngenta*. We hoped to be able to use the rotaxane architecture to modify the physiochemical properties of well known, commercially available herbicides. In addition we hoped that the shielding effect of the macrocycle could reduce the rate of degradation of the active ingredients (AIs) and allow for slow release of the parent herbicides. The herbicides considered in this work, 2,4-D **1** and fluazifop **2**, are not bulky enough to act as stoppering groups alone; we envisaged a design in which herbicide residue(s) attached to the thread at a branch point (Figure 6.3) would provide a sufficiently large barrier to prevent dissociation of the macrocycle and thread.

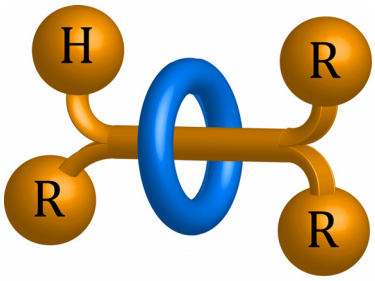


Figure 6.3. Schematic representation of a herbicide containing rotaxane. A macrocycle (blue) encircles a thread (orange) stoppered by at least one herbicide residue (H), the second component at the branch point (R) may be another herbicide residue, a simple bulky group or a bulky group designed to tune the physical properties of the molecule.

Esters of **1** and **2** have been shown to hydrolyze under field conditions to the active parent herbicides,[13] fluazifop is often applied to crops as fluazifop-p-butyl ester **3** due to its more desirable physiochemistry. Therefore we reasoned that an ester linkage could be used to link carboxylic acid herbicides to the thread, allowing for slow release of the herbicide residues after application. The second component at a branch point could take the form of a simple bulky group with no other role other than to hold the rotaxane architecture together. Alternatively, another herbicide residue could be used, increasing the atom economy of the target rotaxanes and allowing the possibility of 'mixed dimers' bearing two types of herbicide residues with different

modes of action or complementary activity spectra. Finally, if necessary the second stopper could be designed to tune the physical properties of the molecule, acting as a solubilizing group for example.

6.2 Results and Discussion

6.2.1 Agrochemical-Based Rotaxanes Assembled Around a Fumaramide Hydrogen Bonding Template

Initially, we decided to make use of a hydrogen bonding template clipping reaction as the key synthetic step in the assembly of the herbicide rotaxanes (*vide supra – Section 1.4.1.1*). The assembly of an amide macrocycle around a rigid fumaramide template[14] in a five component clipping reaction can be performed with readily accessible materials and often proceeds in high yields making it an ideal starting point to investigate the properties of agrochemical-based rotaxanes. Rotaxanes **4**–**6** (Chart 1) were synthesized in a few synthetic steps (*vide infra – Section 6.4*).

The synthesis of the axle precursor of rotaxane **4** was carried out in 5 steps in a good overall yield of 63% however the final rotaxane forming step yielded only 22% of **4**. The reason for the poor recovery of **4** could be in part due to disruption of the hydrogen bond template interaction by the 2,4-dichlorophenoxyacetyl ester groups. However the poor solubility of rotaxane **4** in all common organic solvents is probably the primary reason for the low yield as purification resulted in low recovery of material. Despite these problems enough of rotaxane **4** was obtained to allow preliminary biological tests to be carried out.

The qualified success of the synthesis of **4** encouraged us to pursue a design in which the macrocycle component of the rotaxane would potentially be able to shuttle over areas of the herbicide residues. We were intrigued to see how this encapsulation would affect the degradation and release of the AIs. With this in mind a second design was envisaged, accessed via a short and efficient synthesis from commercially

available (S)-(-)-2-amino-3-phenyl-1-propanol. 2,4-D rotaxane **5** and fluazifop rotaxane **6** were both obtained in reasonable yields with approximately 100 mg of each isolated and submitted for biological testing.

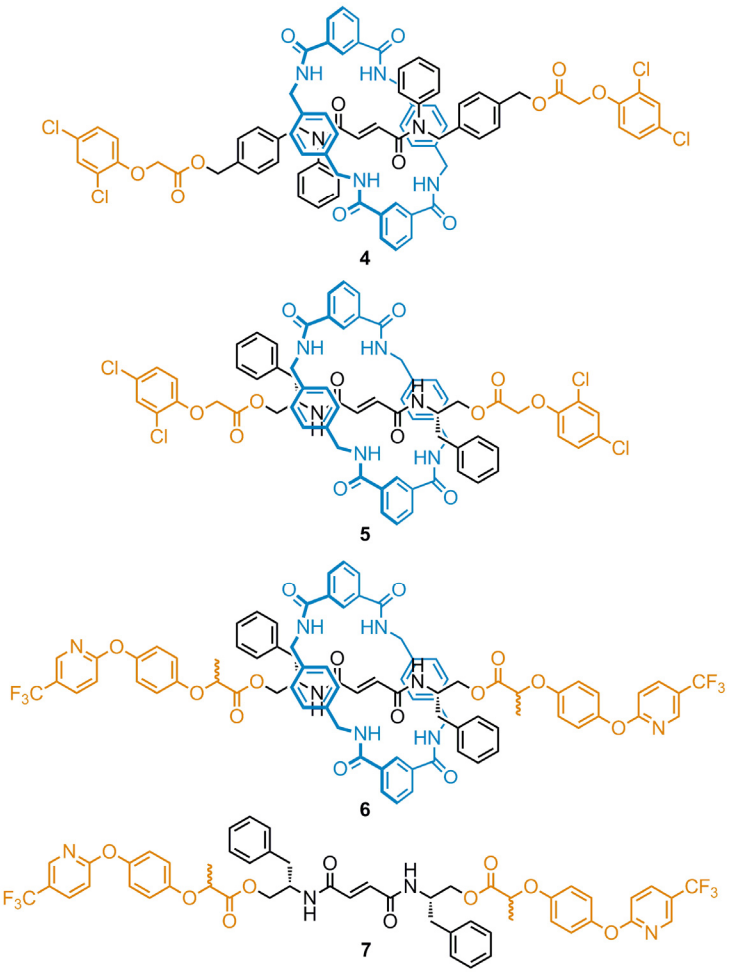


Chart 6.1. Rotaxanes **4–6** synthesized using hydrogen bond directed assembly of the macrocycle (blue) around a fumaramide thread bearing herbicide residues (orange) and thread **7**.

Biological tests were conducted by *Syngenta* with three rates of application for each compound using fluazifop-p-butyl **3** and 2,4-D **1** as standards by which to assess the results. The rates of application were chosen to span the activity expected for the standards so as to show activity at the top rate and to allow for the higher molecular weight and number of AI equivalents in the test compounds. The results of the biological tests are displayed in Table 6.1.

Table 6.1. Herbicidal Activity of Synthesized Compounds **4**–**7** and Commercial Herbicides **1** and **3**.[a]

Entry	Compound	Display Rate / gha^{-1}	Weed Control											
			Post-emergence treatment						Pre-emergence treatment					
			SOLNI	AMARE	IPOHEI	SETFA	ALOMY	ECHCG	SOLNI	AMARE	IPOHEI	SETFA	ALOMY	ECHCG
1	Fusilade-P	250	0	20	0	**100**	**90**	**90**	0	**50**	0	**100**	**90**	**90**
2	Butyl	125	0	0	0	**100**	**90**	**90**	10	**50**	0	**90**	30	**60**
3	**3**	62.5	0	0	0	**90**	**80**	**90**	0	30	0	**90**	20	**50**
4	2,4-D	500	**70**	**100**	**90**	**70**	10	**60**	0	**60**	**60**	10	10	10
5	**1**	250	**50**	**90**	**100**	**60**	10	**40**	0	**40**	20	0	10	0
6		125	**40**	**90**	**80**	30	0	0	0	20	10	0	0	0
7	2,4-D	1620	0	20	30	0	0	0	0	**80**	0	0	0	0
8	Rotaxane	810	0	20	**40**	0	0	0	0	**80**	0	0	0	0
9	**4**	405	0	0	20	0	0	0	0	0	0	0	0	0
10	2,4-D	1480	0	0	**70**	0	0	0	0	0	0	0	0	0
11	Rotaxane	740	0	0	**70**	0	0	0	0	-	0	0	0	0
12	**5**	370	0	-	**70**	0	0	0	0	0	0	0	0	0
13	Fluazifop	500	0	0	0	0	0	0	0	-	0	0	0	0
14	Rotaxane	250	0	0	0	0	0	0	0	0	0	0	0	0
15	**6**	125	0	0	0	0	0	0	0	0	0	0	0	0
16	Fluazifop	320	0	0	0	0	0	0	0	0	0	0	0	0
17	Thread	160	0	0	0	0	0	0	0	0	0	0	0	0
18	**7**	80	0	0	0	0	0	0	0	0	0	0	0	0

[a] Assessment of weed control after 13 days based on visual scale of 0–100 where 0 = no control and 100 = dead plants. Broadleaf weeds; SOLNI = solanum nigrum, AMARE = amaranthus retroflexus, IPOHEI = ipomoea hederacea. Grass weeds; SETFA = setaria faberi, ALOMY = alopecurus myosuroides, ECHCG = echinochloa crus-galli.

The degree of effectiveness of weed control was assessed based on a visual scale of 0 to 100 in which 0 indicates no effect and 100 indicates complete plant death. In order to aid the Reader in the interpretation of these data in Table 6.1, a color code has also been used in which green identifies a high level of weed control, amber indicates a low level and red highlights the cases in which little or no effect was observed. The results obtained for the commercial herbicides used as standards are also shown to allow for comparison. 2,4-D **1** (entries **4**–**6**) is mainly effective when applied to broad-leafed weeds between the emergence of a seedling and maturity (post-emergence) whereas Fusilade-P Butyl **3** (entries **1**–**3**) is somewhat complementary in spectrum, since it is shows activity towards grass weeds when applied both pre- and post-emergence.

Fluazifop rotaxane **6** and the analogous thread **7** both contain two fluazifop residues but nevertheless exhibited no activity (entries **13**–**18**). This can be explained however due to the physical properties of compounds **6** and **7** which presumably resulted in low bioavailability; both compounds were not soluble under the test conditions, in aqueous media. Although the aqueous solubility of 2,4-D rotaxanes **4** and **5** was also very poor there were some interesting, albeit weak, activities (entries **7**–**12**). Both **4** and **5** showed limited activity against broadleaf plants which reflects the selectivity and presumably the mode of action of the parent 2,4-D compound **1**, although the rotaxanes did not demonstrate such a wide spectrum of activity. Intriguingly however, rotaxane **4** shows mostly pre-emergence activity whereas rotaxane **5** shows mostly post-emergence activity. Although the exact reason for this cannot be known with the data currently in hand it is worth noting that in rotaxane **4** the 2,4-D portions of the thread are not encapsulated however in rotaxane **5** at least some of the 2,4-D moiety will be shielded by the macrocycle. This could point to the macrocycle exerting some influence over the kinetics of release of the AI from the rotaxane however the shortage of data prohibits any concrete conclusions been drawn at this stage.

The limiting factor with these initial designs is the poor solubility profile of all the substrates. In order to investigate how the interlocking affects the kinetics of release

of encapsulated herbicide moieties a design is needed that allows access to substrates with lower overall logP values i.e. with improved water solubility. As the fumaramide template and amide macrocycle are responsible in part for the undesirable physical properties of rotaxanes **4**–**6**, we considered other template strategies. We selected the AMT CuAAC reaction[15] as the reaction is also known to be mild and high yielding (*vide supra – Section 1.4.3.2*) and structural features of the macrocycle and 'half-threads' are amenable to alteration, possibly allowing control of the water solubility by variation of one 'half-thread'. In addition, the template interaction between macrocycle and thread does not 'live-on' in the rotaxane, potentially this could allow the macrocycle to encapsulate elements of the herbicide residues more effectively as is can shuttle more freely along the length of the thread.

6.2.2 Agrochemical-Based Rotaxanes Assembled Using the AMT CuAAC Reaction

We explored several designs that could potentially make use of the AMT CuAAC reaction, for ease of synthesis we selected the two designs shown in Figure 6.4. The first design (Figure 6.4a) consists of a 2,6-disubstituted pyridine macrocycle **8**, used effectively in previous AMT CuAAC syntheses,[15,16] and a dumbbell bearing four herbicide residues. The structural similarities of the alkyne and azide 'half-thread' precursors required for this target prompted us to pursue this design at the outset, allowing us to determine whether such a structure could be synthetically accessible. Calculations indicated that the logP of structures of the type shown in Figure 6.4a would still suffer from prohibitively high values; consequently if a viable synthetic route could be established for these structures the next step would be to pursue targets with one solubilizing group 'half-thread' (Figure 6.4b).

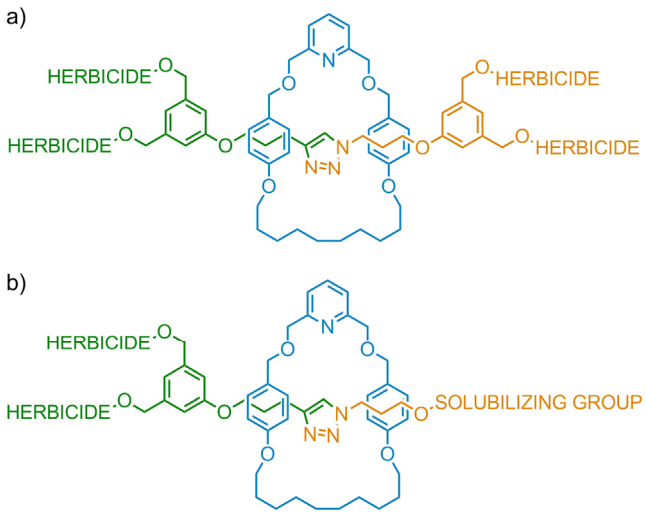
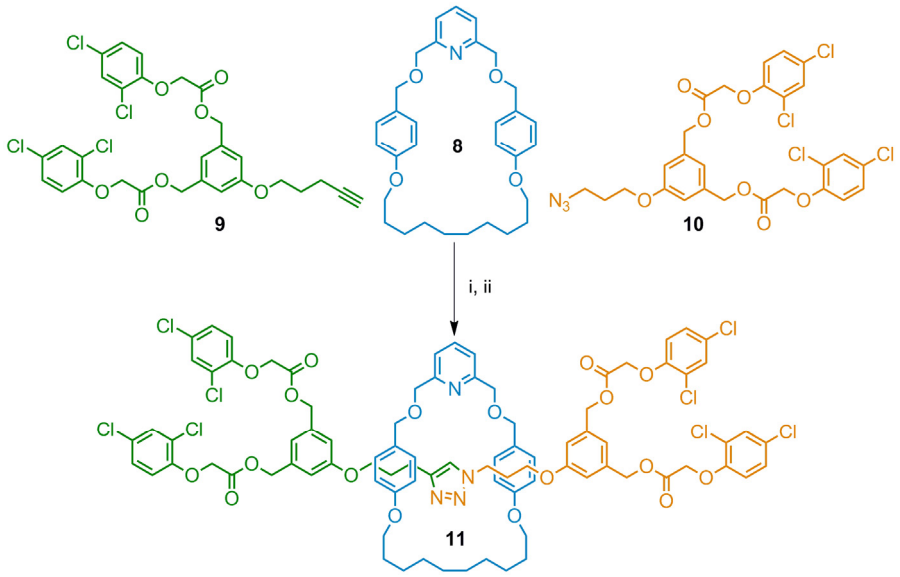


Figure 6.4. Target rotaxanes in which a) two herbicide residues at each end of the thread act as stoppers b) one of the two stoppers consists of a bulky group which can impart favorable physical properties.

Stoppers **9** and **10** were both synthesized in 5 steps from commercial materials in good overall yields – 39% and 35% respectively (*vide infra – Section 6.4*). Pleasingly, reaction between these stoppers (2 molar equivalents of each), with a stoichiometric quantity of $[Cu(CH_3CN)_4](PF_6)$ and pyridyl macrocycle **8** in 1,2-dichloroethane at 70 ºC generated rotaxane **11**, which was isolated after demetallation with a basic ethylenediaminetetraacetic acid-ammonia (EDTA-NH_3) solution (Scheme 6.1). Crucially, we could isolate the target rotaxane **11** in a good yield of 64%, comparable to the literature precedent and high enough to justify further exploration of this strategy.

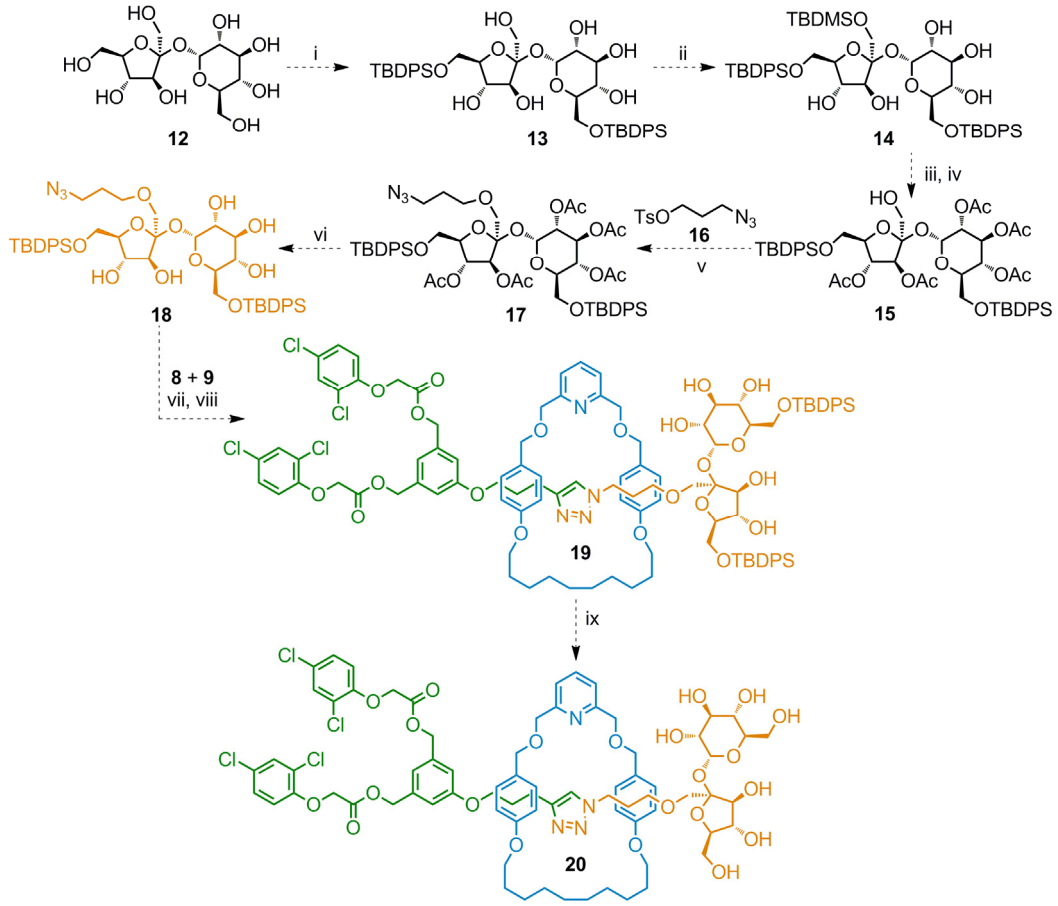
Scheme 6.1. AMT CuAAC synthesis of rotaxane **11** bearing 4 herbicide residues.[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $ClCH_2CH_2Cl$, 70 °C. (ii) EDTA, NH_3, 64%.

This brief foray into the assembly of agrochemical-based rotaxanes using the AMT strategy established that the necessary precursors and final targets can be synthesized via concise, high-yielding pathways. However, our overriding aim was to use this template strategy as a means to produce rotaxanes that would be amenable to biological assessment, i.e. with a good degree of water solubility. In the pursuit of this goal we chose to focus our attention towards designing a polar azide that could participate in a CuAAC AMT reaction to form a rotaxane—acting as a 'solubilizing stopper'. Synthetic studies towards this target have not yet been initiated however the synthetic route envisaged is presented in Scheme 6.2. We selected a design based around sucrose, hoping that the multiple hydroxyl groups of the disaccharide would impart good water solubility and that protective group manipulations known in the literature[17] could allow functionalization at the 1′ position. Connecting the thread to the sucrose moiety at the 1′ position—creating a 'branch point' between the pyranose and furanose ring—would provide a suitably bulky 'sucrose stopper' to prevent the macrocycle from dethreading.

Scheme 6.2. Planned synthesis of sucrose stoppered rotaxane **20**.[a]



[a] Reagents and conditions: (i) TBDPSCl, pyridine, 4-dimethylaminopyridine, 60 °C, 24 h. (ii) TBDMSCl, pyridine, 4-dimethylaminopyridine, rt, 24 h. (iii) Acetic anhydride, pyridine. (iv) I_2, MeOH, Δ, 1 h. (v) NaH, DMF, Δ. (vi) NaOMe(cat.), CH_2Cl_2-MeOH, rt. (vii) $[Cu(CH_3CN)_4](PF_6)$, $ClCH_2CH_2Cl$, 70 °C. (viii) EDTA, NH_3. (ix) TBAF, THF, 0 °C.

The synthetic route we envisaged proceeds through key intermediate **15**, a known compound that can be prepared according to a series of protective group manipulations, in which the 1′ position exclusively bears a free hydroxyl group. TBDPS protecting groups can be installed selectively on the least hindered primary hydroxyl groups (6- and 6′ positions) to give **13** which can be taken on to **14** by formation of a TBDMS ether on the remaining primary alcohol. Per-acetylation of the residual secondary alcohols is then followed by selective cleavage of the TBDMS ether to furnish **15**. We then plan to alkylate under Williamson conditions with toluene-4-sulfonic acid 3-azido-propyl ester **16**[15a] prior to hydrolysis of the acetyl esters to reveal the secondary alcohol groups. At this stage we intend to leave the

TBDPS ethers intact and use pentol **18** directly in the AMT CuAAC reaction with macrocycle **8** and 2,4-D alkyne stopper **9** to generate rotaxane **19**. We reason that cleavage of the TBDPS ethers prior to this step would be likely to result in a material which would not be soluble under the standard conditions employed for the AMT CuAAC reaction. The final stage of the synthesis will be deprotection of the two remaining silyl ethers to liberate rotaxane **20** with a 1′ substituted sucrose stopper and two 2,4-D residues.

6.3 Conclusions and Outlook

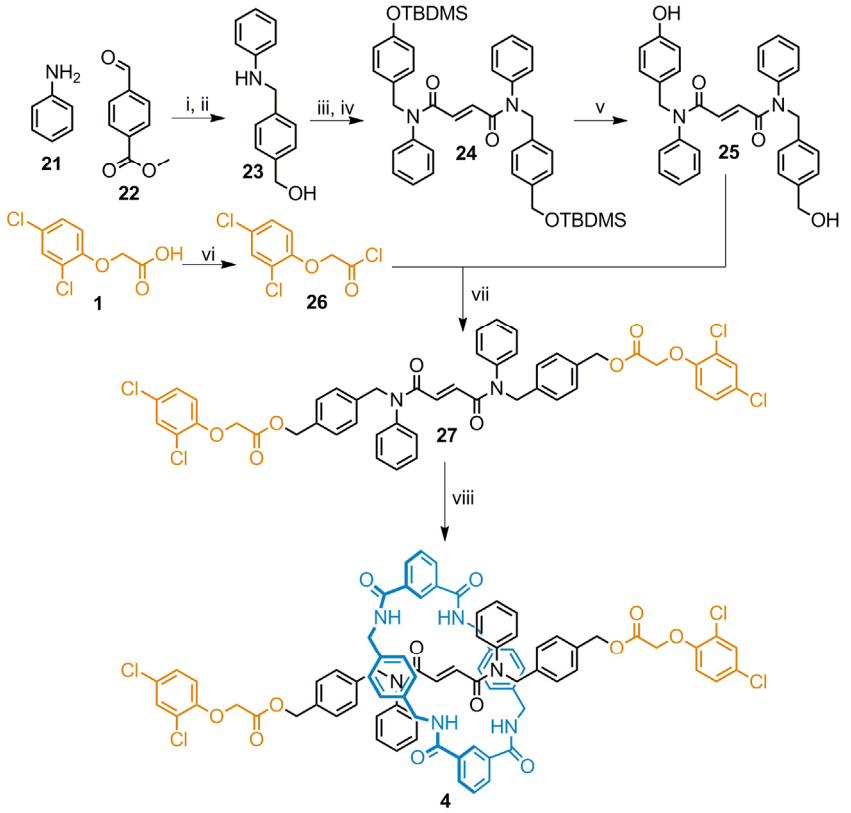
We have successfully synthesized a number of agrochemical-based rotaxanes and assessed some of these for herbicidal activity. Two of the herbicide rotaxanes assembled around a fumaramide hydrogen bond template motif demonstrated interesting herbicidal activity however their undesirable physical properties precluded further analysis. We then investigated the AMT strategy as a means to construct herbicide rotaxanes with improved water solubility. The successful, high yielding synthesis of rotaxane **11** via an AMT CuAAC reaction confirmed that this synthetic approach is indeed viable. Work is currently underway into the synthesis of a 'sucrose stopper' that we hope to be able to use to construct rotaxane **20**. Should we be able to synthesize this target we intend to assess its herbicidal activity in comparison with the less polar analogue **11**.

6.4 Experimental Details

Pyridyl macrocycle **8**,[18] toluene-4-sulfonic acid pent-4-ynyl ester **37**[15b] and toluene-4-sulfonic acid 3-azido-propyl ester **16**[15a] were prepared according to literature procedures.

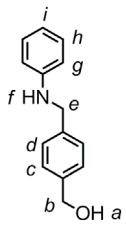
6.4.2 Synthesis of Rotaxane 4

Scheme 6.3. Synthesis of Rotaxane **4** from Aniline **21** and Methyl 4-Formylbenzoate **22**.[a]



[a] Reagents and conditions: (i) MeOH, -18 °C, 18 h. (ii) $LiAlH_4$, THF, 0 °C → rt, 1 h, 85% over 2 steps. (iii) imidazole, TBDMSCl, DMF, 50 °C, 12 h. (iv) fumaryl dichloride, Et_3N, CH_2Cl_2, 2 h, 81% over 2 steps. (v) TBAF, THF, 0 °C → rt, 2 h, 94%. (vi) $SOCl_2$, DMF(cat.), THF, rt, 30 min. (vii) THF, Et_3N, rt, 30 min, 98%. (viii) p-Xylenediamine, isophthaloyl dichloride, Et_3N, $CHCl_3$, rt, 4 h, 22%.

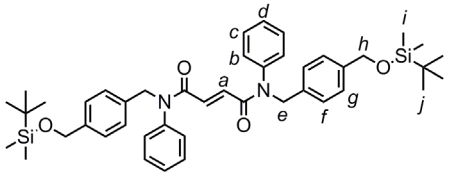
(4-Phenylaminomethyl-phenyl)-methanol



23

To a solution of methyl 4-formylbenzoate **22** (2.50 g, 15.2 mmol) in MeOH (20 ml) at rt was added aniline **21** (1.42 g, 15.2 mmol) and the mixture was cooled to -18 °C and stirred for 1 h. A white precipitate formed which was collected by suction filtration and washed with ice cold MeOH (5 mL). The solid was dried under reduced pressure then dissolved in THF (300 mL) and cooled to 0 °C. To this stirred solution was added slowly $LiAlH_4$ (3.46 g, 91.2 mmol) and the resulting suspension allowed to warm to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C and H_2O (3.5 mL) was added dropwise followed by a solution of NaOH (15% by weight, 3.5 mL) then H_2O (10.5 mL). The suspension was filtered through celite and the filtrate dried ($MgSO_4$) and the solvent removed under reduced pressure to give amine **23** (2.8 g, 85%) as a colorless solid. M.p. 50–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 4H, H_c + H_d), 7.17 (dd, 2H, J = 7.4, J = 8.5, H_h), 6.72 (t, 1H, J = 7.3, H_i), 6.63 (d, 2H, J = 7.6, H_g), 4.69 (s, 2H, H_b), 4.34 (s, 2H, H_e), 4.05 (bs, 1H, H_f); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.0, 139.8, 138.9, 129.2, 127.6, 127.3, 117.5, 112.8, 65.1, 47.9; LREI-MS: *m/z* = 213 $[M]^+$; HREI-MS: *m/z* = 213.1147 $[M]^+$ (calcd. for $C_{14}H_{15}NO$ 213.1148).

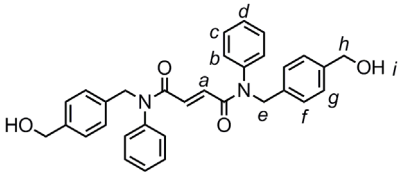
(E)-But-2-enedioic acid bis-{[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-benzyl]-phenyl-amide}



24

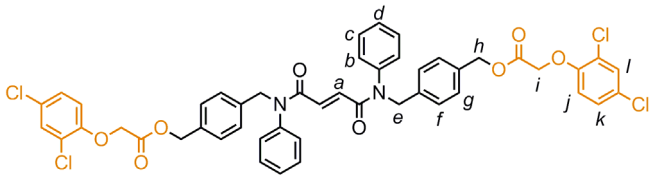
To a solution of amine **23** (1.387 g, 6.5 mmol) in DMF (3.25 ml) at rt was added imidazole (487 mg, 7.15 mmol) and TBDMSCl (1.078 g, 7.15 mmol) and the mixture was heated at 50 °C for 12 h. The reaction mixture was cooled to rt and diluted with Et_2O (150 mL) and washed with H_2O (3 × 150 mL portions). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was diluted with CH_2Cl_2 (28 mL) and to the resulting solution was added Et_3N (2 mL) then fumaryl dichloride (879 mg, 5.75 mmol) portion wise. The solution was stirred at rt for 2 h then diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2 × 50 mL) then brine (50 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (CH_2Cl_2-acetone 9:1) gave fumaramide thread **24** (1.9 g, 81%) as a yellow solid. M.p 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 6H, H_b + H_d), 7.14 (dd, 8H, J = 8.0, J = 32.5, H_f + H_g), 6.96 (dd, 4H, J = 1.8, J = 7.5, H_c), 6.88 (s, 2H, H_a), 4.88 (s, 4H, H_h), 4.68 (s, 4H, H_e), 0.91 (s, 18H, H_j), 0.06 (s, 12H, H_i); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 141.1, 140.6, 135.4, 132.0, 129.6, 128.5, 128.0, 126.0, 64.6, 53.2, 30.9, 30.2, 25.9; LRFAB-MS (3-NOBA matrix): *m/z* = 735 $[M\text{H}]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 735.4009 $[M\text{H}]^+$ (calcd. for $C_{44}H_{59}O_4N_2Si_2$ 735.4008).

(E)-But-2-enedioic acid bis-[(4-hydroxymethyl-benzyl)-phenyl-amide]



25

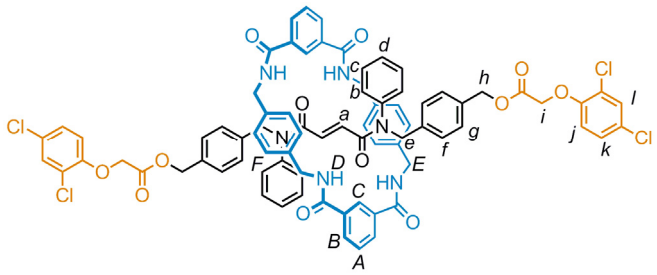
To a solution of fumaramide thread **24** (992 mg, 1.35 mmol) in THF (50 mL) at 0 °C was added TBAF (5.4 mL, 1M in THF) and the resulting mixture stirred at rt for 2 h. The solvent was removed under reduced pressure and chromatography of the resulting residue (1. CH_2Cl_2-MeOH 98:2, 2. CH_2Cl_2-MeOH 94:6) yielded diol **25** (640 mg, 94%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (m, 6H, H_b + H_d), 7.17 (m, 8H, H_c + H_g), 7.07 (d, 4H, J = 7.9, H_f), 6.68 (m, 2H, H_a), 4.89 (s, 4H, H_h), 4.42 (d, 4H, J = 5.7, H_e); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD 1:1) δ 133.3, 131.0, 129.9, 129.7, 129.3, 128.3, 65.2, 59.9, 54.5, 25.0, 20.9, 14.5; LRFAB-MS (3-NOBA matrix): m/z = 507 $[MH]^+$; HRFAB-MS (3-NOBA matrix): m/z = 507.2279 $[MH]^+$ (calcd. for $C_{32}H_{31}O_4N_2$ 507.2278).



26

To a solution of 2,4-dichlorophenoxyacetic acid **1** (524 mg, 2.37 mmol) in THF (5 mL) with a drop of DMF at rt was added $SOCl_2$ (564 mg, 4.74 mmol) and the resulting mixture stirred for 30 min. The solvent and excess $SOCl_2$ was removed under reduced pressure. The resulting residue was dissolved in THF (5 mL) and to this solution was added Et_3N (242 mg, 2.37 mmol) and a solution of diol **25** (200 mg, 395 μmol) in THF (5 mL). The mixture was stirred at rt for 30 min then diluted with EtOAc (40 mL) and extracted with 1M $HCl_{(aq)}$ (2 × 50 mL portions) and brine (50

mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (1. CH_2Cl_2, 2. CH_2Cl_2-EtOAc 9:1) of the resulting residue yielded diester **26** (359 mg, 98%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H, H_b + H_d + H_l), 7.14 (m, 10H, H_f + H_g + H_k), 6.98 (dd, 4H, J = 1.9, J = 7.5, H_c), 6.88 (s, 2H, H_a), 6.71 (d, 2H, J = 8.8, H_j), 5.16 (s, 4H, H_h), 4.90 (s, 4H, H_e), 4.69 (s, 4H, H_i); LRFAB-MS (3-NOBA matrix): m/z = 913 $[M^{35}Cl_3{}^{37}ClH]^+$; HRFAB-MS (3-NOBA matrix): m/z = 913.1439 $[M^{35}Cl_3{}^{37}ClH]^+$ (calcd. for $C_{48}H_{39}O_8N_2{}^{35}Cl_3{}^{37}Cl$, 913.1431).



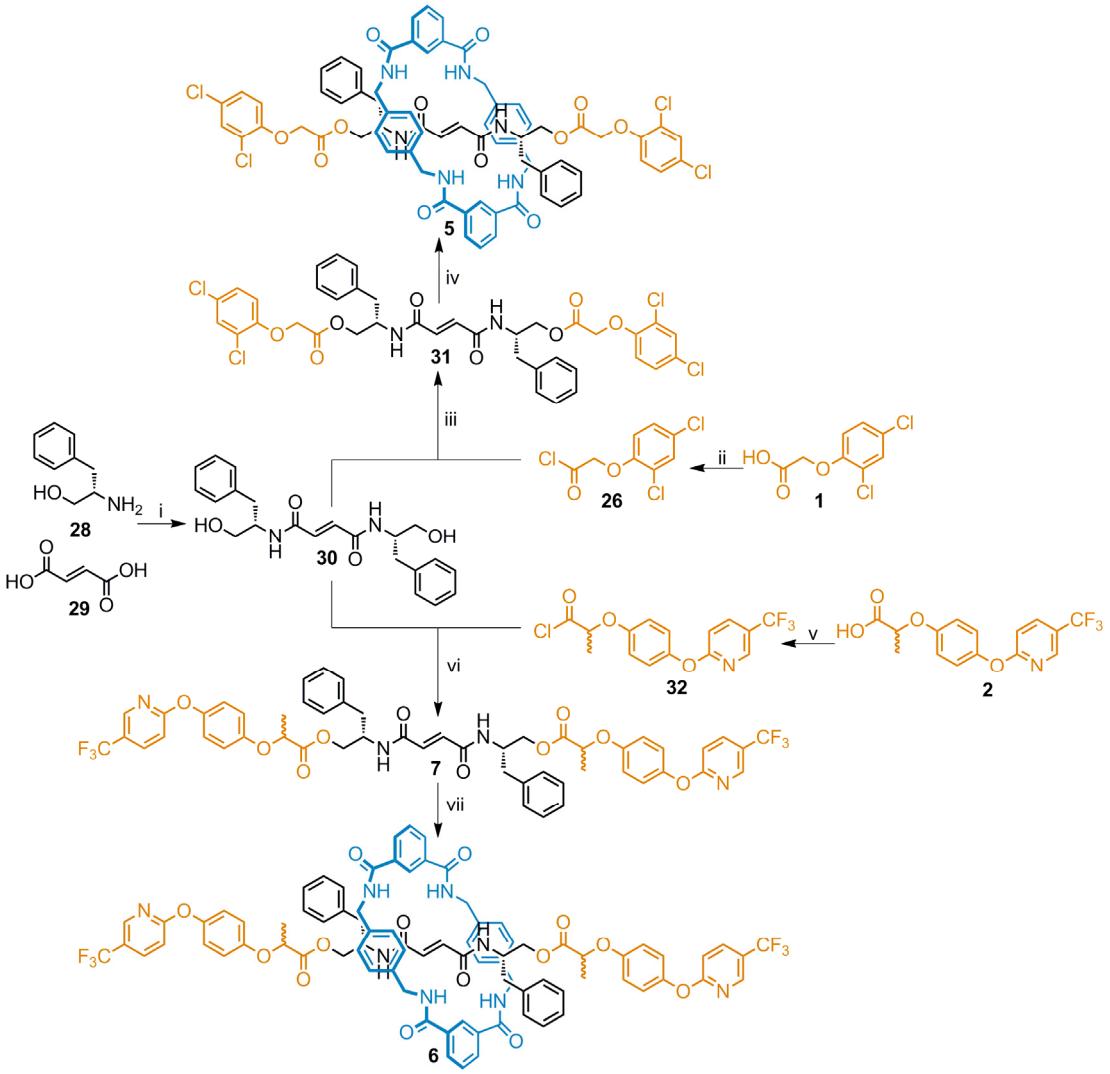
4

2,4-D thread **26** (283 mg, 311 μmol) and Et_3N (1.01 g, 9.95 mmol) were dissolved in $CHCl_3$ (30 mL) and the mixture was stirred vigorously while solutions of the p-xylenediamine (678 mg, 4.98 mmol) in $CHCl_3$ (10 mL) and isophthaloyl dichloride (1.01 g, 4.98 mmol) in $CHCl_3$ (10 mL) were simultaneously added over a period of 4 h using motor-driven syringe pumps. A white precipitate formed which was removed by suction filtration through celite, washing with 7:3 $CHCl_3$-IPA. The solvent was removed from the filtrate under reduced pressure then chromatography of the residue (1. CH_2Cl_2-EtOAc 9:1, 2. CH_2Cl_2-EtOAc, 4:1) gave 2,4-D rotaxane **4** (97 mg, 22%) as a colorless solid. M.p 195–197 °C. ^{1}H NMR (400 MHz, 1 $CDCl_3$) δ 8.27 (dd, 1H, J = 1.4, J = 7.7, H_B), 8.07 (s, 2H, H_C), 7.65 (t, 2H, J = 7.8, H_A), 7.25 (d, 2H, J = 2.5, H_l), 7.07 (m, 8H, H_f + H_g), 7.00 (dd, 2H, J = 2.5, J = 8.8, H_k), 6.91 (t, 4H, J = 7.9, H_c), 6.79 (m, 12H, H_F + H_b), 6.66 (d, 2H, J = 8.8, H_j), 6.41 (t, 2H, J = 7.5, H_d), 5.44 (s, 2H, H_a), 5.14 (dd, 8H, J = 9.3, J = 14.0, H_E), 5.12 (s, 4H, H_h), 4.69 (s, 4H, H_e), 4.62 (s, 4H, H_i), 3.41 (dd, 4H, J = 1.5, J = 14.1, H_D); LRFAB-MS (3-NOBA matrix):

m/z = 1443 $[MH]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 1443.3710 $[MH]^+$ (calcd. for $C_{80}H_{67}O_{12}N_6{}^{35}Cl_4$, 1443.3571).

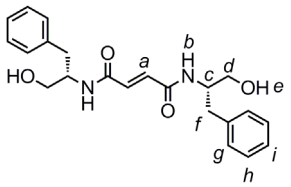
6.4.2 Synthesis of Rotaxanes 5 and 6

Scheme 6.4. Synthesis of Rotaxanes **5** and **6**.[a]



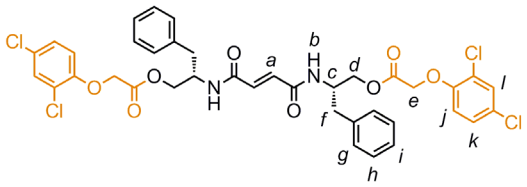
[a] Reagents and conditions: (i) EDCI, HOBt, DIPEA, DMF, 0 °C → rt, 12 h, 89%. (ii) $SOCl_2$, DMF(cat.), THF, rt, 30 min. (iii) DMF, Et_3N, rt, 2 h, 53%. (iv) p-Xylenediamine, isophthaloyl dichloride, Et_3N, $CHCl_3$, rt, 4 h, 36%. (v) $SOCl_2$, DMF(cat.), THF, rt, 30 min. (vi) DMF, Et_3N, rt, 2 h, 89%. (vii) p-Xylenediamine, isophthaloyl dichloride, Et_3N, $CHCl_3$, rt, 4 h, 14%.

(E)-But-2-enedioic acid bis-[((S)-1-benzyl-2-hydroxy-ethyl)-amide]



30

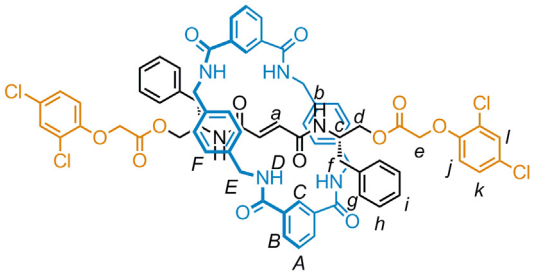
To a stirred solution of (S)-(-)-2-amino-3-phenyl-1-propanol **28** (1.00 g, 6.60 mmol), EDCI (1.39 g, 7.30 mmol), HOBt (990 mg, 7.30 mmol) and DIPEA (1.88 g, 14.5 mmol) in DMF (20 mL) at 0 °C was added fumaric acid **29** (380 mg, 0.33 mmol) and the resulting mixture stirred at rt for 12 h. H_2O (10 mL) was added causing a white precipitate to form. The precipitate was isolated by suction filtration washing on the filter with EtOAc (10 mL) and Et_2O (10 mL) then dried under reduced pressure giving diol **30** (1.112 g, 89%) as a colorless solid that was used without further purification. M.p 205–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1) δ 7.20 (m, 10H, $H_g + H_h + H_i$), 6.75 (m, 2H, H_a), 4.17 (m, 2H, H_c), 3.54 (m, 4H, H_d), 2.84 (ddd, 4H, J = 7.2, J = 13.8, J = 21.5, H_f); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD 1:1) δ 165.8, 138.7, 133.3, 129.7, 128.9, 126.9, 63.3, 53.9, 37.3; LRESI-MS: *m/z* = 384 $[MH]^+$; HRESI-MS: *m/z* = 383.1967 $[MH]^+$ (calcd. for $C_{22}H_{27}O_4N_2$ 383.1965).



31

To a solution of 2,4-dichlorophenoxyacetic acid **1** (1.04 g, 4.70 mmol) in THF (10 mL) with a drop of DMF at rt was added $SOCl_2$ (1.12 g, 9.41 mmol) and the resulting mixture stirred for 30 min. The solvent and excess $SOCl_2$ was removed under reduced pressure. The resulting residue was dissolved in DMF (5 mL) and to this solution was added Et_3N (480 mg, 4.70 mmol) and a solution of diol **30** (300 mg, 780

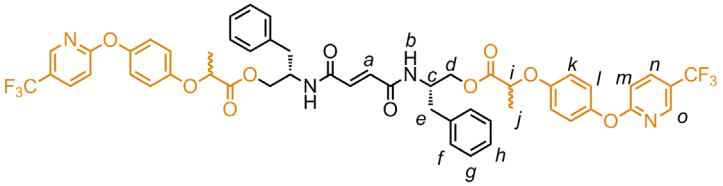
μmol) in DMF (5 mL). The mixture was stirred at rt for 2 h then diluted with EtOAc (40 mL) and extracted with 1M $HCl_{(aq)}$ (2 × 50 mL portions), saturated $NaHCO_{3(aq)}$ (2 × 50 mL portions) and brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (1. CH_2Cl_2-EtOAc 4:1, 2. CH_2Cl_2-EtOAc 1:1) of the resulting residue yielded diester **31** (325 mg, 53%) as a yellow solid. M.p 189 – 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1) δ 7.34 (d, 2H, J = 2.5, H_l), 7.20 (m, 12H, H_g + H_h + H_i + H_k), 6.84 (d, 2H, J = 8.8, H_j), 6.74 (s, 2H, H_a), 4.73 (s, 4H, H_e), 4.45 (m, 2H, H_c), 4.33 (dd, 2H, J = 4.0, J = 11.3, H_d), 4.08 (m, 2H, $H_{d'}$), 2.83 (d, 4H, J = 7.3, H_f); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD 1:1) δ 169.1, 165.6, 153.0, 137.6, 133.3, 130.7, 129.7, 129.6, 129.1, 128.9, 128.3, 127.3, 115.3, 66.5, 66.2, 50.6, 37.5.



5

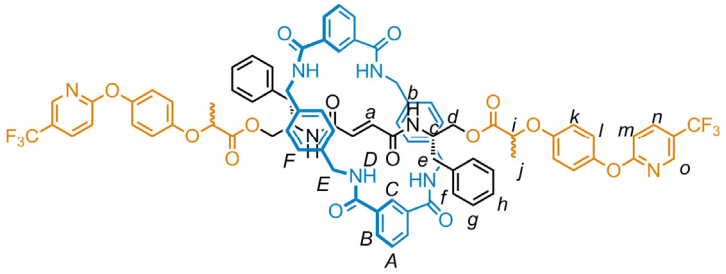
The 2,4-D thread * (287 mg, 380 μmol) and Et_3N (1.22 g, 12.0 mmol) were dissolved in $CHCl_3$ (60 mL) and the mixture was stirred vigorously while solutions of the p-xylenediamine (817 mg, 6.00 mmol) in $CHCl_3$ (20 mL) and isophthaloyl dichloride (1.22 g, 6.00 mmol) in $CHCl_3$ (20 mL) were simultaneously added over a period of 4 h using motor-driven syringe pumps. A white precipitate formed which was removed by suction filtration through celite, washing with $CHCl_3$-IPA 7:3. The solvent was removed from the filtrate under reduced pressure then chromatography of the residue (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2-MeOH 95:5) gave 2,4-D rotaxane **5** (173 mg, 36%) as a colorless solid. M.p 163–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1) δ 8.48 (m, 2H, H_C), 8.09 (dd, 4H, J = 1.0, J = 7.8, H_B), 7.62 (t, 2H, J = 7.8, H_A), 7.33 (m, 2H, H_l), 7.30–7.05 (m, 12H, H_g + H_h + H_i + H_k), 6.78 (m, 2H, H_j), 6.72 (s,

8H, H_F), 5.61 (s, 2H, H_a), 4.67 (m, 4H, H_e), 4.41 (m, 4H, H_E), 4.20 (m, 4H, $H_{E'}$), 4.12 (m, 4H, H_d + H_c), 4.03 (m, 2H, $H_{d'}$), 2.85 (m, 2H, H_f), 2.66 (m, 2H, $H_{f'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.0, 137.8, 137.2, 134.5, 131.7, 130.7, 130.5, 129.8, 129.5, 129.4, 129.3, 128.2, 127.7, 125.8, 115.3, 66.5, 66.1, 66.1, 51.4, 44.4, 30.1, 29.8, 19.0; LRFAB-MS (3-NOBA matrix): *m/z* = 1321 $[M^{35}Cl_3{}^{37}ClH]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 1321.3244 $[M^{35}Cl_3{}^{37}ClH]^+$ (calcd. for $C_{70}H_{63}O_{12}N_6{}^{35}Cl_3{}^{37}Cl$, 1321.3229).



7

To a solution of a racemic mixture of fluazifop **2** (1.53 g, 4.70 mmol) in THF (10 mL) with a drop of DMF at rt was added $SOCl_2$ (1.12 g, 9.41 mmol) and the resulting mixture stirred for 30 min. The solvent and excess $SOCl_2$ was removed under reduced pressure. The resulting residue was dissolved in DMF (5 mL) and to this solution was added Et_3N (480 mg, 4.70 mmol) and a solution of diol **30** (300 mg, 780 μmol) in DMF (5 mL). The mixture was stirred at rt for 2 h then diluted with EtOAc (40 mL) and extracted with H_2O (2 × 50 mL portions), saturated $NaHCO_{3(aq)}$ (2 × 50 mL portions) and brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (1. CH_2Cl_2-EtOAc 9:1, 2. CH_2Cl_2-EtOAc 4:1) of the resulting residue yielded diester **7** (695 mg, 89%) as a white solid which was an inseparable mixture of two diasteroisomers, submitted for biological testing without further purification. M.p 169–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1) δ 8.28 (m, 2H, H_m), 7.88 (m, 2H, H_n), 7.24 - 6.88 (m, 20H, H_f + H_g + H_h + H_k + H_l + H_o), 6.73 (m, 2H, H_a), 4.81 (m, 2H, H_i), 4.42 (m, 2H, H_c), 4.21 (m, 2H, H_d), 4.11 (m, 2H, $H_{d'}$), 2.77 (m, 4H, H_e), 1.60 (m, 6H, H_j).

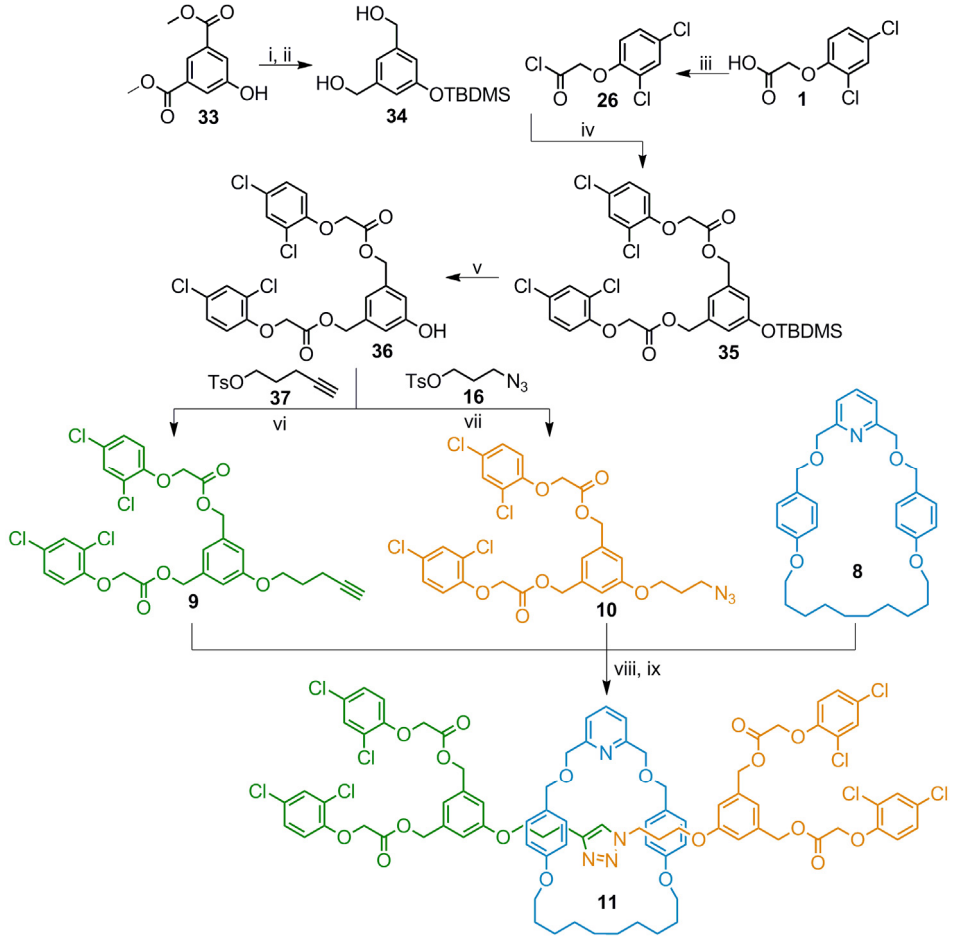


6

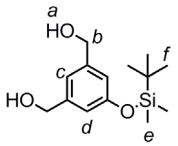
The fluazifop thread **7** (597 mg, 600 μmol) and Et_3N (1.96 g, 19.2 mmol) were dissolved in $CHCl_3$ (90 mL) and the mixture was stirred vigorously while solutions of the p-xylenediamine (1.30 g, 9.60 mmol) in $CHCl_3$ (30 mL) and isophthaloyl dichloride (1.95 g, 9.60 mmol) in $CHCl_3$ (30 mL) were simultaneously added over a period of 4 h using motor-driven syringe pumps. A white precipitate formed which was removed by suction filtration through celite, washing with $CHCl_3$-IPA 7:3. The solvent was removed from the filtrate under reduced pressure then chromatography of the residue (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2-MeOH 95:5) gave fluazifop rotaxane **6** (124 mg, 14%) as a colorless solid which was an inseparable mixture of two diasteroisomers, submitted for biological testing without further purification. M.p 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 1:1) δ 8.61 (m, 4H, $H_C + H_m$), 8.18 (m, 8H, $H_B + H_B$), 7.86 (m, 2H, H_n), 7.54 (m, 2H, H_A), 7.30-6.86 (m, 20H, $H_f + H_g + H_h + H_k + H_l + H_o$), 6.64 (s, 8H, H_F), 5.64 (d, 2H, $J = 1.7$, H_a), 4.83 (m, 2H, H_i), 4.36 (m, 4H, H_E), 4.16 (m, 11H, $H_{E'} + H_c + H_d$), 4.00 (m, 2H, $H_{d'}$), 2.79 (m, 2H, H_e), 2.58 (m, 2H, $H_{e'}$), 1.59 (dd, 6H, $J = 4.5$, $J = 6.7$, H_j); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD 1:1) δ 172.9, 172.8, 168.0, 166.4, 155.7, 148.1, 145.7, 138.2, 137.7, 137.3, 134.5, 134.2, 132.0, 130.0, 129.7, 129.5, 129.2, 127.8, 125.8, 123.3, 117.0, 116.7, 111.8, 75.9, 73.6, 69.8, 66.6, 54.1, 52.7, 51.8, 44.4, 37.1, 30.9, 22.1, 18.9, LRFAB-MS (3-NOBA matrix): *m/z* = 1534 $[M^{13}CH]^+$; HRFAB-MS (3-NOBA matrix): *m/z* = 1534.5346 $[M^{13}CH]^+$ (calcd. for $C_{83}H_{75}{}^{13}CO_{14}N_8F_6$ 1534.5341).

6.4.3 Synthesis of Rotaxane 11

Scheme 6.5. Synthesis of Rotaxane **11** From Dimethyl 5-Hydroxy-Isophthalate **33**.[a]



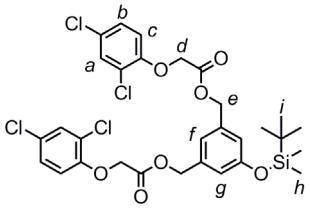
[a] Reagents and conditions: (i) imidazole, TBDMSCl, DMF, 50 °C, 12 h. (ii) $LiAlH_4$, THF, 0 °C → rt, 4 h, 67% over 2 steps. (iii) $SOCl_2$, DMF(cat.), THF, rt, 30 min. (iv) THF, Et_3N, rt, 18 h, 83%. (v) TBAF, THF, 0 °C, 15 min, 76%. (vi) Cs_2CO_3, DMF, 55 °C, 3 h, 93%. (vii) Cs_2CO_3, DMF, 55 °C, 3 h, 83%. (viii) $[Cu(CH_3CN)_4](PF_6)$, $ClCH_2CH_2Cl$, 70 °C. (ix) EDTA, NH_3, 64%.



34

To a solution of dimethyl 5-hydroxy-isophthalate **33** (500 mg, 2.4 mmol) in DMF (1.6 ml) at rt was added imidazole (178 mg, 2.6 mmol) and TBDMSCl (395 mg, 2.6 mmol) and the mixture was heated at 50 °C for 12 h. The reaction mixture was cooled

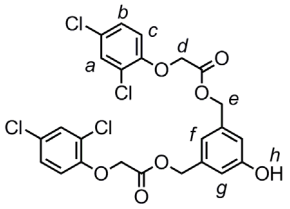
to rt and diluted with Et_2O (30 mL) and washed with H_2O (3 × 30 mL portions). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was then dissolved in THF (25 mL) and cooled to 0 °C. To this stirred solution was added slowly $LiAlH_4$ (537 mg, 14.1 mmol) and the resulting suspension allowed to warm to rt and stirred for 4 h. The reaction mixture was cooled to 0 °C and H_2O (0.5 mL) was added dropwise followed by a solution of NaOH (15% by weight, 1.5 mL) then H_2O (1.5 mL). The suspension was filtered through celite and the filtrate dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography of the residue (gradient elution: 1. CH_2Cl_2, 2. CH_2Cl_2-EtOAc 4:1) gave dialcohol **34** (431 mg, 67%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H, H_c), 6.78 (s, 2H, H_d), 4.65 (s, 4H, H_b), 0.98 (s, 9H, H_f), 0.20 (s, 6H, H_e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 142.7, 118.1, 117.7, 65.1, 25.6, 17.8, -4.4; LREI-MS: *m/z* = 268 $[M]^+$; HREI-MS: *m/z* = 268.1489 $[M]^+$ (calcd. for $C_{14}H_{24}O_3Si$ 268.1489).



35

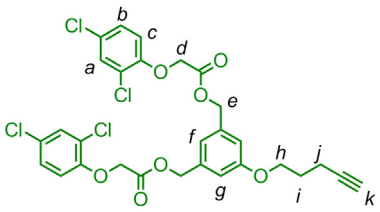
To a solution of 2,4-dichlorophenoxyacetic acid **1** (1.33 g, 6 mmol) in THF (20 mL) with a drop of DMF at rt was added $SOCl_2$ (1.43 g, 12 mmol) and the resulting mixture stirred for 30 min. The solvent and excess $SOCl_2$ was removed under reduced pressure. The resulting residue was dissolved in THF (20 mL) and to this solution was added Et_3N (610 mg, 6 mmol) and diol **34** (400 mg, 1.5 mmol). The mixture was stirred at rt for 18 h then diluted with EtOAc (40 mL) and extracted with 1M $HCl_{(aq)}$ (2 × 50 mL portions), saturated $NaHCO_{3(aq)}$ (2 × 50 mL portions) and brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (CH_2Cl_2-petrol 1:1) of the resulting residue yielded diester **35** (1.24 g, 83%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.39 (d, J = 2.5, 2H, H_a), 7.13 (dd, J = 8.8, 2.5, 2H, H_b), 6.88 (s, 1H, H_f), 6.80–6.72 (m, 4H, H_c + H_g), 5.15 (s, 4H, H_d), 4.73 (s, 4H, H_e), 0.98 (s, 9H, H_i), 0.18 (s, 6H, H_h); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 154.9, 152.2, 137.7, 130.3, 127.5, 127.1, 124.2, 120.5, 116.2, 115.3, 66.4, 66.3, 25.7, 17.8, -4.5; LREI-MS: m/z = 672 $[M]^+$; HREI-MS: m/z = 672.0669 $[M]^+$ (calcd. for $C_{30}H_{32}O_7Cl_4Si$ 672.0666).



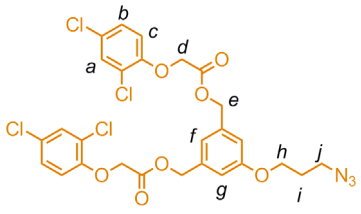
36

To a solution of TBDMS ether **35** (652 mg, 0.97 mmol) in THF (60 mL) at 0 °C was added TBAF (0.97 mL, 1M in THF) and the resulting mixture stirred at 0 °C for 15 min. The reaction mixture was diluted with EtOAc (30 mL) and extracted with H_2O (2 × 50 mL portions) and brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the resulting residue (1. CH_2Cl_2, 2. CH_2Cl_2-EtOAc 19:1) yielded phenol **36** (414 mg, 76%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 2.5, 2H, H_a), 7.17–7.09 (m, 2H, H_b), 6.84 (s, 1H, H_f), 6.79–6.70 (m, 4H, H_c + H_g), 5.15 (s, 4H, H_d), 4.73 (s, 4H, H_e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 156.0, 152.2, 137.1, 130.3, 127.5, 127.1, 124.2, 120.2, 115.3, 114.6, 66.4, 66.3; LRESI-MS: m/z = 559 $[M\text{-H}]^-$; HRESI-MS (3-NOBA matrix): m/z = 560.9873 $[M\text{H}]^+$ (calcd. for $C_{24}H_{19}O_7{}^{35}Cl_3{}^{37}Cl$ 560.9855).



9

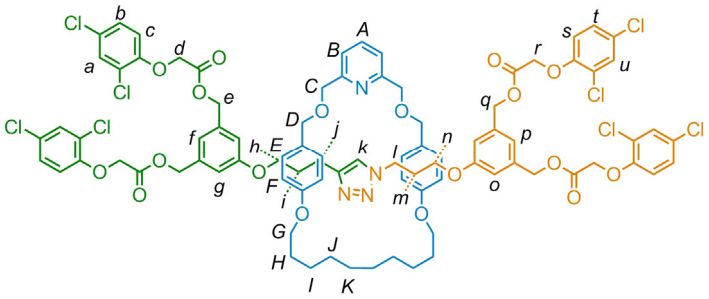
Toluene-4-sulfonic acid pent-4-ynyl ester **37**[15b] (84 mg, 350 µmol) was added to a solution of phenol **36** (50 mg, 90 µmol) and Cs_2CO_3 (58 mg, 180 µmol) in DMF (2 mL) and the reaction mixture heated to 55 °C for 3 h. The reaction mixture was then allowed to cool to rt and EtOAc (40 mL) and H_2O (40 mL) were added. The phases were separated and the organic phase was washed with H_2O (3 x 40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1. CH_2Cl_2-petrol 1:1, 2. CH_2Cl_2) to give alkyne stopper **9** (52 mg, 93%) as a gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.5, 2H, H_a), 7.14 (dd, *J* = 8.8, 2.5, 2H, H_b), 6.85 (s, 1H, H_f), 6.83 (s, 2H, H_g), 6.75 (d, *J* = 8.8, 2H, H_c), 5.18 (s, 4H, H_d), 4.74 (s, 4H, H_e), 4.03 (t, *J* = 6.0, 2H, H_h), 2.42 (td, *J* = 6.9, 2.6, 2H, H_j), 2.07–1.93 (m, 3H, H_i + H_k); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 159.3, 152.2, 136.8, 130.4, 127.5, 127.1, 124.2, 120.2, 114.6, 114.4, 83.3, 77.3, 77.0, 76.7, 69.1, 66.6, 66.3, 28.0, 15.1; LRESI-MS: *m/z* = 625 [*M*H]$^+$.



10

Toluene-4-sulfonic acid 3-azido-propyl ester **16**[15a] (69 mg, 270 µmol) was added to a solution of phenol **36** (100 mg, 180 µmol) and Cs_2CO_3 (117 mg, 360 µmol) in DMF

(4 mL) and the reaction mixture heated to 55 °C for 3 h. The reaction mixture was then allowed to cool to rt and EtOAc (40 mL) and H_2O (40 mL) were added. The phases were separated and the organic phase was washed with H_2O (3 x 40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1. petrol-EtOAc 9:1, 2. petrol-EtOAc 4:1) to give azide stopper **10** (95 mg, 83%) as a gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.5, 2H, H_a), 7.13 (dd, *J* = 8.8, 2.5, 2H, H_b), 6.87 (s, 1H, H_f), 6.82 (s, 2H, H_g), 6.74 (d, *J* = 8.8, 2H, H_c), 5.18 (s, 4H, H_d), 4.74 (s, 4H, H_e), 4.00 (t, *J* = 5.9, 2H, H_h), 3.52 (t, *J* = 6.6, 2H, H_j), 2.05 (m, 2H, H_i); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 159.1, 152.2, 136.9, 130.4, 127.5, 127.1, 124.2, 120.4, 114.6, 114.3, 66.6, 66.3, 64.6, 48.1, 28.7; LRESI-MS: *m/z* = 642 $[M\text{H}]^+$.



11

Alkyne **9** (36.0 mg, 57.5 µmol) and azide **10** (37.0 mg, 57.5 µmol) were added to a solution of macrocycle **8** (14.0 mg, 28.7 µmol) and $[Cu(CH_3CN)_4](PF_6)$ (10.7 mg, 28.7 µmol) in $ClCH_2CH_2Cl$ (1 mL). The solution was heated to 70 ºC and allowed to stir at this temperature for 18 h. The reaction mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (20 mL). This organic phase was washed with a 17.5% solution of NH_3 saturated with EDTA (3 x 20 mL), water (20 mL) then brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative TLC on silica gel (1. petrol-EtOAc 2:1, 2. petrol-EtOAc 1:1) gave rotaxane **11** (32 mg, 64%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (br, 1H, H_A), 7.37 (d, *J* = 2.5, 4H, H_a + H_u), 7.31 (br, 2H, H_B), 7.12 (dd, *J* = 8.8, 2.5, 4H, H_b + H_t), 7.02 (d, *J* = 7.8, 4H, H_E), 6.95 (br, 1H, H_k), 6.84 (s,

2H, $H_f + H_p$), 6.79–6.57 (m, 12H, $H_c + H_g + H_o + H_s + H_F$), 5.15 (s, 8H, $H_d + H_r$), 4.74 (s, 4H, H_e or H_q), 4.72 (s, 4H, H_e or H_q), 4.50 (s, 4H, H_D), 4.31 (s, 4H, H_C), 3.91–3.82 (m, 6H, $H_G + H_n$), 3.73 (t, J = 6.2, 2H, H_h), 3.36 (t, J = 5.1, 2H, H_l), 2.59 (t, J = 7.6, 2H, H_j), 1.88 (m, 2H, H_i), 1.73–1.62 (m, 8H, $H_m + H_H$), 1.44–1.09 (m, 12H, $H_I + H_J + H_K$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.3, 158.8, 158.7, 152.2, 146.5, 136.7, 130.3, 130.0, 127.5, 127.1, 127.1, 124.2, 124.2, 121.3, 120.2, 120.0, 114.7, 114.7, 114.4, 114.4, 114.2, 72.7, 67.1, 67.0, 66.7, 66.6, 66.3, 66.3, 64.3, 46.3, 29.7, 29.6, 28.7, 28.6, 28.6, 25.7, 21.9 –due to pseudo-symmetry of rotaxane **11** only 28 distinct signals observed of the possible 48 inequivalent carbon nuclei. LRESI-MS: m/z = 1756 $[M^{13}CH]^+$.

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CHAPT. 7 | SUMMARY AND OUTLOOK

This Thesis has highlighted several recent advances in the AMT methodology that have been achieved in the period of September 2007 – July 2010. The AMT concept had been conceived within the preceding three years but had already undergone rapid development. At the outset of the research discussed in this Thesis a number of AMT reactions had already been established that employed Cu^{I} or Pd^{II} as the macrocycle-bound metal ion, mediating a variety of connective reactions based on well-known transformations. The most pertinent of these with regards to this Thesis was the AMT CuAAC reaction which had been thoroughly investigated and served as a springboard for much of the work discussed herein. During the same time frame of this Thesis advances continued in parallel which sustained the theme of reaction development, several other AMT reactions were reported which expanded the scope of the AMT strategy to include Ni^{II} and Zn^{II} promoted couplings such as Michael addition and Diels–Alder cycloaddition.

Chapter 2 of this Thesis described the development of a novel Ni-catalyzed sp^3-carbon-to-sp^3-carbon homocoupling of unactivated alkyl bromides and its application to the active metal template synthesis of an alkyl chain axle [2]rotaxane. The significance of this work lies not only in the discovery of a new reaction but perhaps more importantly in the manner in which it was discovered. For the first time the exploration of the AMT strategy brought about unexpected results which in turn led to the discovery of a functional new reaction. Although this finding was entirely unplanned it perhaps foreshadows the shape of future work in this area. Further investigation into the AMT ‘catalysis within cavities’ may serve as a conduit for reaction discovery and—by the nature of the geometric restraints imposed by the macrocyclic ligands—lead to the elucidation of the mechanisms that underpin these transformations.

A feature of the AMT methodology that sets it apart from traditional template approaches to the synthesis of MIMs is the ability of the metal ion to ‘turn over’ which allows for the use of a catalytic amount of template to be used. The potential of this characteristic to allow the assembly of more complex architectures around a

single template site was demonstrated by the work reported in *Chapter 3*. The synthesis of homo- and hetero-macrobicyclic [3]rotaxanes was described in which one active template site on the bridging portion of a macrobicycle mediated the sequential formation of a thread component in each of the two cavities. In addition to acting as a proof-of-principle for this particular aspect of the AMT strategy the information gained on the relationship between the cavity size and the allosteric regulation between cavities may be put to use in the design of more elaborate systems.

In September 2007, the AMT approach had only been applied to the synthesis to the rotaxane class of interlocked molecules. *Chapters 4 and 5* described the application of the AMT philosophy to the assembly of two classes of topologically complex molecules – [2]catenanes and a trefoil knot. It was discovered that [2]catenanes could be successfully accessed in good yields using both a single and double macrocyclization approach to assemble the interlocking rings. As might be expected for such macrocyclization reactions, the product distribution was found to be concentration dependent; less predictably however the choice of AMT reaction was found to be pivotal as the functional groups present in the acyclic precursors were required to withstand protracted reaction times at elevated temperatures. This discovery impacted directly on the design of the trefoil knot presented in *Chapter 5*, prompting the choice of an AMT CuAAC reaction for the key knot forming step due to the high stability and exceptional fidelity of the alkyne and azide functional groups required. The strategy presented here made use of two Cu^{I} ions that work in tandem to entangle an acyclic building block and covalently capture the knotted architecture. NMR analysis of the isolated product strongly supports the formation of the desired trefoil—the world's smallest knot—however it is hoped that this can be shown unambiguously through X-ray crystallography.

Chapter 6 described the design, template-directed synthesis and biological assessment of rotaxanes bearing herbicidal motifs. The motivation for this work came from the ability of the macrocyclic component of a rotaxane to alter the physical

properties and chemical stability of the encapsulated thread. We hoped to be able to use these characteristics to modify the physiochemical properties of well known, commercially available herbicides. In addition we hoped that the shielding effect of the macrocycle could reduce the rate of degradation of the active ingredients and allow for slow release of the parent herbicides. This work produced a number of rotaxanes which demonstrated interesting herbicidal activity, however their undesirable physical properties (poor solubility) precluded further analysis.

In 2010 there is certainly still room to broaden scope of AMT reactions which will undoubtedly increase the tool box available for the construction of rotaxanes, catenanes and knots and further expand the range of functional groups which can be used in their construction. Most notably there is a glaring omission in the range of metal ions which have been harnessed in AMT reactions to date – Pd^0. The addition of Pd^0 coupling reactions to the roster of AMT reactions would surely be of particular worth owing to their versatility and utility in organic synthesis. Stepping away from transition metal catalysis altogether, opportunities also lie in the field of organocatalysis. The AMT concept could readily be extended to this area through the design of macrocycles with suitable endotopic functionality.

The current arsenal of AMT reactions could also be put to good use in the synthesis of hard-to-access structures which would be difficult or impossible to access by traditional means. Architectures with multiple interlocked components or without strong inter-component interactions and residual template sites could be assembled through careful macrocycle design and application of the lessons learned about the requirements and tolerances of AMT reactions developed in the last five years.

APPENDIX | PUBLISHED PAPERS

'Ligand-assisted nickel-catalysed sp^3–sp^3 homocoupling of unactivated alkyl bromides and its application to the active template synthesis of rotaxanes'– Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, *1*, 383–386.

'Two Axles Threaded Using a Single Template Site: Active Metal Template Macrobicyclic [3]Rotaxanes' – Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315–320.

'Active Metal Template Synthesis of [2]Catenanes'– Goldup, S. M.; Leigh, D. A.; Long, T.; McGonigal, P. R.; Symes, M. D.; Wu, J. *J. Am. Chem. Soc.* **2009**, *131*, 15924–15929.

Ligand-assisted nickel-catalysed sp^3–sp^3 homocoupling of unactivated alkyl bromides and its application to the active template synthesis of rotaxanes†

Stephen M. Goldup,[a] David A. Leigh,*[a] Roy T. McBurney,[a] Paul R. McGonigal[a] and Andrew Plant[b]

Received 25th April 2010, Accepted 28th May 2010
DOI: 10.1039/c0sc00279h

An efficient, mild and operationally simple Ni-catalysed sp^3-carbon-to-sp^3-carbon homocoupling of unactivated alkyl bromides has been developed and utilised in the active metal template synthesis of an alkyl chain axle [2]rotaxane. The key to the transformation is the use of tridentate nitrogen-donor-atom (terpy or pybox derived) ligands which inhibit competing β-hydride elimination of alkyl-Ni intermediates.

Introduction

Several of the earliest rotaxanes to be rationally synthesised consisted of rings threaded onto simple alkyl chain axles terminated by bulky 'stoppering' groups.[1] The subsequent development[2] of template approaches dramatically increased the efficiency of rotaxane forming reactions,[3] however usually at the cost that permanent recognition elements to direct the interlocking need to be built into both components. Active template methods,[4,5] in which transition metal ions act as both the template for the threaded architecture and as the catalyst for the covalent bond forming reaction that captures the interlocked structure, remove the requirement for a recognition motif in the thread. Nevertheless, the active template synthesis of alkyl chain rotaxanes has not previously been demonstrated, in part because sp^3–sp^3 C–C bond forming reactions are particularly challenging to achieve. Here we describe an active template rotaxane-forming reaction that achieves this difficult construction using a Ni-mediated homocoupling of bromoalkanes. The search for a successful active template system for alkyl chain rotaxane synthesis led to the discovery of this potentially useful catalytic transformation—a novel, mild dehalogenative homocoupling of unactivated alkyl bromides.

Transition metal catalysed sp^3-carbon to sp^3-carbon bond forming reactions

The paucity of effective, catalytic, transition-metal-mediated sp^3–sp^3 C–C bond forming reactions is largely due to the slow rates of oxidative addition of metal centres to sp^3-carbon–halogen (and other heteroatom) bonds and the propensity of the resulting organometallic intermediates to undergo β-hydride elimination.[6,7] Successful sp^3-carbon-to-sp^3-carbon coupling protocols are generally limited to halides that are activated towards oxidative addition and lack β-hydrogen atoms (for example, allylic and benzylic chlorides).[8] Recently, the coupling of unactivated alkyl halides with alkyl organometallics under mild conditions using highly reactive Pd and Ni catalysts has been reported.[9–12] The Ni-mediated reactions disclosed[11,12] by Fu and co-workers are particularly noteworthy as they allow racemic secondary bromides to be cross-coupled with alkyl nucleophiles with excellent enantioselectively.[12]

Results and discussion

Active template synthesis of an alkyl chain axle rotaxane

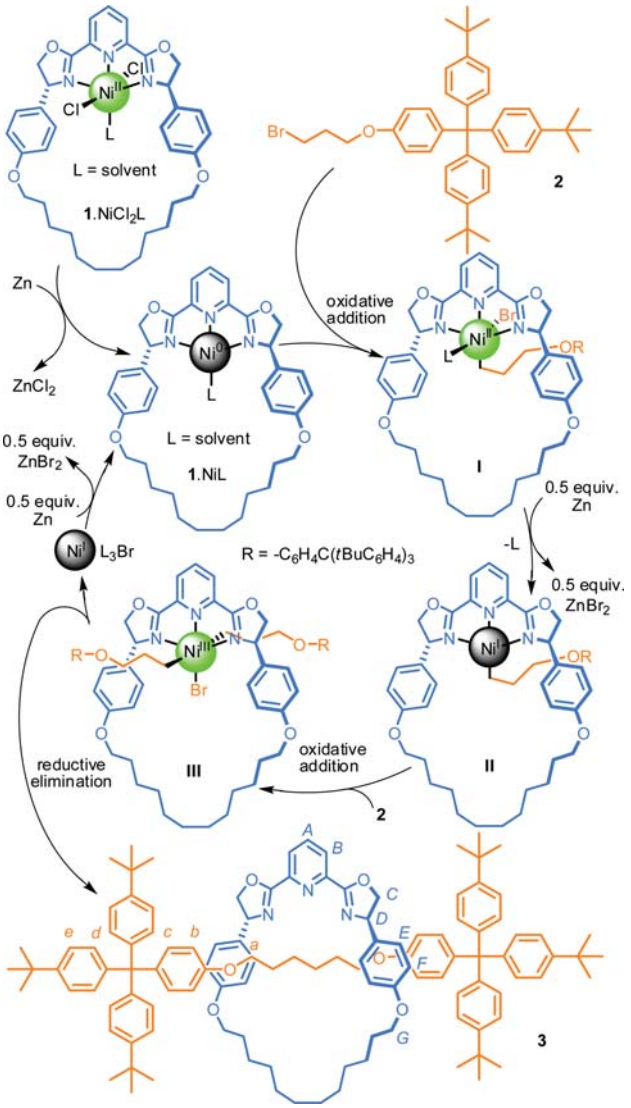
We chose the Negishi system developed by Fu and co-workers as a starting point for our investigations into an active template alkyl-chain-forming reaction as it employs a pyridine-2,6-bisoxazoline (pybox) ligand[12] that molecular modeling indicated[13] could create a rigid endotopic coordination site when incorporated into an appropriate macrocyclic scaffold. Macrocycle **1** was synthesised in 10 steps from commercially available materials (see ESI†).

We initially focused on the reaction of a bulky alkyl bromide with its corresponding zincate—effectively a homocoupling as the zincate is derived from the bromide—reasoning that the formation of the zincate and the subsequent Ni-mediated coupling reaction might be carried out simultaneously in one pot. Pleasingly, stirring macrocycle **1**, 1 equiv. of $NiCl_2 \cdot DME$ (dimethoxyethane) and 2.2 equiv. of bromide **2** in the presence of 4 equiv. of activated Zn in THF–*N*-methyl-2-pyrrolidone (NMP) at 80 °C over 18 h led to the formation of [2]rotaxane **3** (Scheme 1), as evidenced by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry. Although ^{1}H NMR spectroscopy indicated complete consumption of macrocycle **1**, isolation of [2]rotaxane **3** proved difficult as the pybox moiety of the macrocycle was unstable to chromatography on silica gel and also, to some extent, to the conditions of the reaction itself. Purification using reverse phase silica gel gave a modest isolated rotaxane yield of 24%.

Somewhat surprisingly, when the reaction protocol was modified to employ the preformed zincate of **2**,[14] no product was observed. This strongly implied that the homocoupling reaction was not in fact proceeding *via* a Negishi manifold.[7,12] Replacing activated Zn with Mn powder in the original procedure gave a similar yield of rotaxane **3**, indicating that the homocoupling

[a]*School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh, UK EH9 3JJ. E-mail: David.Leigh@ed.ac.uk; Fax: +44 (0) 131-650-6453; Tel: +44 (0) 131-650-4721*
[b]*Syngenta Crop Protection, Münchwilen AG, WST-810.3.38, 4332 Stein, Switzerland*

† Electronic supplementary information (ESI) available: Synthesis and characterisation of all compounds. CCDC reference number 774871. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0sc00279h



Scheme 1 Rotaxane synthesis *via* a novel Ni-mediated active template sp^3-carbon–sp^3-carbon coupling reaction. Reagents and conditions: (i) **2** (2.2 equiv.), $NiCl_2 \cdot DME$ (1 equiv.), Zn (4 equiv.), NMP–THF (1 : 1), 80 or 25 °C, 18 h, 24% (80 °C) or 46% (25 °C).

reaction does not involve transmetallation of an alkyl organometallic species to Ni, as the formation of RMnX from Mn(0) should not occur to a significant extent under these conditions.[15,16] Lowering the reaction temperature to 25 °C increased the yield of [2]rotaxane **3** to 46%, further evidence that formation of RZnX is not required for the homocoupling reaction.[17]

The results of these experiments are consistent with the mechanistic pathway shown in Scheme 1, in which Ni(II)-alkyl species **I**—produced by oxidative addition of the alkyl bromide to **1**·Ni(0)L—is reduced to the Ni(I)-intermediate **II** by Zn, which then oxidatively adds to another equivalent of the alkyl bromide. The isolation of the interlocked product indicates that this oxidative addition must proceed through the cavity of the macrocycle to give threaded complex **III** which then reductively eliminates in a concerted fashion to give [2]rotaxane **3**. The resulting Ni(I) complex can then be reduced to Ni(0) by Zn and restart the catalytic cycle.[18] This mechanism is similar to that

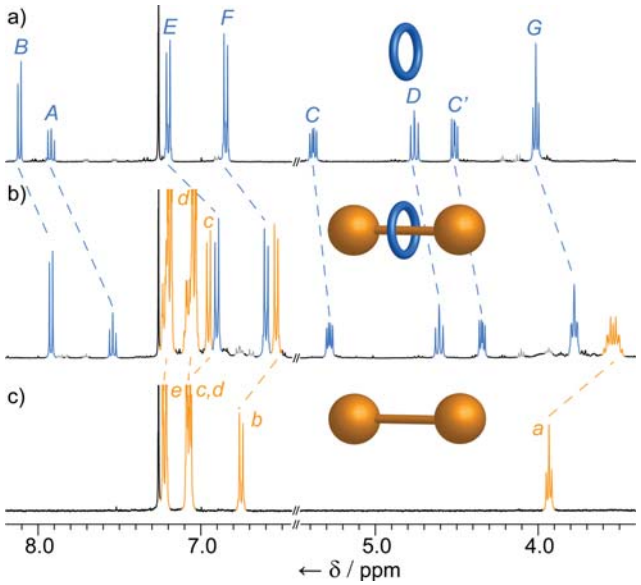


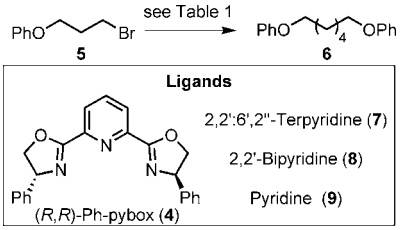
Fig. 1 Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) macrocycle **1**, (b) [2]rotaxane **3**, and (c) non-interlocked thread. The assignments correspond to the lettering shown in Scheme 1.

accepted for the Ni-mediated coupling of aryl halides[19] and that proposed for the dehalogenative cross-coupling of aryl and alkyl halides.[15]

The interlocked structure of [2]rotaxane **3** was confirmed by comparison of its ^{1}H NMR spectrum with the spectra of the corresponding non-interlocked macrocycle (**1**) and thread (Fig. 1). The shielding effects typical of face-on interactions of aromatic rings in interlocked architectures are observed for several of the resonances present in **3**. Furthermore the signal corresponding to H_a is more complex in the rotaxane than the thread due to the chiral environment of the macrocycle which renders these protons diastereotopic.

General Ni-catalysed sp^3-carbon–sp^3-carbon homocoupling of unactivated alkyl bromides

Although metal-promoted sp^2-carbon–sp^2-carbon homocouplings are well known,[20] the metal-catalysed sp^3-carbon–sp^3-carbon homocoupling of unactivated alkyl halides has not previously been described.[18,21] The classic Wurtz coupling[22] can bring about this type of transformation, but it is seldom used in a practical context as it requires stoichiometric quantities of highly reactive metals (*e.g.* Na) and normally gives low yields due to competing elimination and rearrangement processes. The harsh conditions for Wurtz couplings are only compatible with a few functional group types, a problem shared by sp^3-carbon–sp^3-carbon bond forming reactions between Grignard reagents and alkyl halides or sulfonates. One of the most popular ways to couple molecular fragments *via* an sp^3-carbon–sp^3-carbon bond is through ring closing (intramolecular) or cross (intermolecular) olefin metathesis followed by hydrogenation of the resulting internal alkene.[23] Accordingly, a mild general method for the dehalogenative homocoupling of unactivated alkyl bromides to form C–C bonds potentially has wide practical utility and so we performed an optimisation study (Scheme 2, Table 1) on the



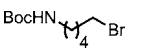
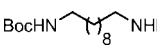
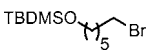
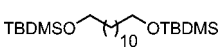
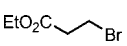
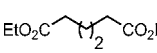
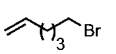
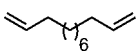
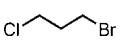
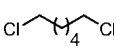
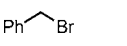
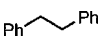
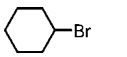
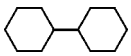
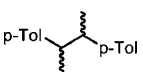
Scheme 2 Ligand-assisted Ni-catalysed homocoupling of 1-bromo-3-phenoxypropane. For reagents and conditions see Table 1.

Table 1 Optimisation of the conditions, ligand and nickel source for the Ni-catalysed homocoupling of 1-bromo-3-phenoxypropane (Scheme 2)

Entry	Ni source (mol%)	Ligand	Yield/%	Time/h
1[a]	$NiCl_2$·DME (50)	**4**	>95[c]	18
2[a]	$NiCl_2$·DME (12.5)	**4**	>95[c]	18
3[a]	$NiCl_2$·DME (5)	**4**	93[d]	18
4[a]	$NiCl_2$·DME (2.5)	**4**	50[c]	18
5[a]	$NiCl_2$·DME (5)	**7**	86[d]	18
6[a]	$NiCl_2$·$(H_2O)_6$ (5)	**7**	88[d]	18
7[b]	$NiCl_2$·$(H_2O)_6$ (5)	**7**	95[d]	18
8[b]	$NiCl_2$·$(H_2O)_6$ (5)	**7**	95[d]	1
9[b]	$NiCl_2$·$(H_2O)_6$ (5)	**8**	<5[c]	18
10[b]	$NiCl_2$·$(H_2O)_6$ (5)	**9**	<5[c]	18
11[b]	$NiCl_2$·$(H_2O)_6$ (5)	—	0	18

[a] Reagents and conditions: (i) **5** (1 equiv.), Zn (1 equiv.), NMP–THF (1 : 1), rt. [b] DMF. [c] Yield assessed by GCMS analysis. [d] Isolated yield.

Table 2 Substrate scope for the 2,2′:6′,2″-terpyridine (**7**)-assisted Ni-catalysed homocoupling of alkyl bromides[a]

Entry	Substrate	Product	Yield/%
1			97
2			96
3[b]			78
4			>99
5			>99
6			95
7			>99
8			80[c]

[a] $NiCl_2$·$(H_2O)_6$, 2,2′:6′,2″-terpyridine **7**, DMF, 4 h, rt. [b] 18 h. [c] 1 : 1 mixture of diastereoisomers. *p*-Tol = 4-CH_3-C_6H_4–.

catalytic protocol discovered above and explored the generality of the transformation (Table 2).

When 1-bromo-3-phenoxypropane **5** was treated with Ni(II) and acyclic pybox ligand **4** (replacing macrocycle **1**), under the conditions developed for the active template reaction, **6** was isolated in essentially quantitative yield (>95%, Table 1, entry 1). This indicates that the homocoupling reaction itself is extremely efficient and supports the notion that the yield of rotaxane **3** is limited by the stability of the macrocycle under the reaction conditions. It proved possible to reduce the loading of Ni(II) to 5 mol% (entry 3) without any significant reduction in product yield, but lower catalyst loadings were less effective (entry 4). Replacing chiral ligand **4** with achiral tridentate ligand 2,2′:6′,2″-terpyridine (**7**) led to a slight reduction in yield (entry 5) which was improved when cheap, air stable, $NiCl_2$·$(H_2O)_6$ was substituted for air sensitive $NiCl_2$·DME (entry 6). Changing the solvent to DMF improved both the reaction yield with the $NiCl_2$·$(H_2O)_6$ catalyst (entry 7) and the reaction rate (entry 8). The crucial role played by the tridentate ligand[10] (**4** or **7**) was demonstrated by control reactions with bidentate (**8**) and monodentate (**9**) analogues (entries 9 and 10) or the absence of any ligand (entry 11), each of which resulted in virtually no product being formed.

The substrate scope of the reaction was also investigated (Table 2). The reaction tolerates standard oxygen and nitrogen function protecting groups well (entries 1 and 2), including modestly acidic NH groups (entry 1) and esters (entry 3; longer reaction times were required here, possibly due to chelation of the Ni by the ester carbonyl). Alkenyl substrates are also compatible with the reaction (entry 4). The absence of cyclopentane by-products when using this substrate suggests that radical pathways are not in operation[10] during the oxidative addition and reductive elimination steps, a finding reinforced by the formation of the threaded product during the active template reaction (Scheme 1). Clear selectivity between C–Br and C–Cl bonds is demonstrated by the chemoselective reaction of 1,3-chlorobromopropane (entry 5). Homocoupling of benzyl bromide proceeds in high yield (entry 6) and coupling of bromocyclohexane is essentially quantitative (entry 7), showing that secondary alkyl bromides are also highly effective substrates for this reaction. Although the dimerisation of a racemic secondary bromide proceeded in good yield (entry 8), no selectivity between the chiral and *meso* diastereoisomers was observed (d.r. = 1 : 1). Repeating this reaction using (*R*,*R*)-Ph-pybox **4** gave no change in the diastereoisomeric ratio, suggesting that the stereoconvergent process demonstrated[12] by Fu and co-workers in their Negishi cross-couplings of racemic alkyl halides does not appear to operate in this system.

Conclusions

Through the search for an sp^3-carbon–sp^3-carbon bond forming active template reaction to produce an alkyl chain axle rotaxane, we have developed a high yielding general method for the homocoupling of primary and secondary alkyl bromides. This ligand-assisted nickel-catalysed procedure is operationally simple, efficient and cheap and may prove to be broadly applicable. Active template rotaxane synthesis not only represents an advanced strategy for the construction of mechanically interlocked molecules but, as exemplified here, can also serve as an effective conduit for reaction discovery.[5]

Acknowledgements

We thank Drs Hon Lam and Mike Greaney (Edinburgh) for useful discussions, Syngenta for a PhD studentship (to PRM)

and the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) for mass spectrometry. DAL is an EPSRC Senior Research Fellow and holds a Royal Society-Wolfson research merit award.

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J|A|C|S ARTICLES

Published on Web 12/07/2009

Two Axles Threaded Using a Single Template Site: Active Metal Template Macrobicyclic [3]Rotaxanes

Stephen M. Goldup,† David A. Leigh,*,† Paul R. McGonigal,† Vicki E. Ronaldson,† and Alexandra M. Z. Slawin‡

School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom, and School of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife KY16 9ST, United Kingdom

Received September 22, 2009; E-mail: David.Leigh@ed.ac.uk

Abstract: Template approaches to rotaxanes normally require at least $n - 1$ template sites to interlock n components. Here we describe the one-pot synthesis of [3]rotaxanes in which a single metal template site induces formation of axles through each cavity of a bicyclic macrocycle. Central to the approach is that a portion of the bicyclic molecule acts as a ligand for a transition metal ion that mediates covalent bond formation through one or other macrocyclic cavity, depending on the ligand's orientation, making a mechanical bond. The ligand can then rotate so that the transition metal can catalyze the formation of a second axle through the other macrocycle. Using this strategy with the Cu(I)-catalyzed azide−alkyne cycloaddition (the CuAAC reaction) generates a [3]rotaxane with two identical axles in up to 86% yield. [3]Rotaxanes with two different axles threaded through the macrobicyclic rings can also be created using a single template site, either by having copper(I) sequentially form both mechanical bonds (via the CuAAC reaction) using different sets of building blocks for each axle or by using two different reactions catalyzed by two different metal ions: a palladium(II)-mediated alkyne homocoupling to assemble the first thread through one cavity, followed by a copper(I)-mediated CuAAC reaction to form the second axle through the other ring.

Introduction

In recent years, template strategies have allowed increasingly elaborate structures featuring multiple mechanical bonds to be constructed.[1] Various examples of rotaxanes,[2] pseudorotaxanes,[3] catenanes,[4] and other types[5] of molecular links with three or more mechanical bonds or components have been described. Systems with multiple mechanical bonds between components that are also covalently connected have also been prepared.[6−8] However, the vast majority of [n]rotaxanes with $n > 2$ components consist of $n - 1$ rings encircling a single thread (linear[2a,c,h,j,m−o,q] or branched[2b,e,j−l,p]), while rotaxanes consisting of multiple threads passing through rings are still rare.[2j,r,u,w] A feature common to almost[2n] all these synthetic strategies is that at least $n - 1$ template sites are normally required to interlock n components. Here we report on the synthesis of [3]rotaxanes in which a single metal template site sequentially induces formation of an axle through each cavity of a bicyclic ring system. The methodology relies on "active template"[9] rotaxane formation, in which a coordinated metal ion acts as both the template for the interlocked product and as a catalyst for promoting the formation of the crucial covalent bond that captures the threaded architecture. Active template synthesis has previously been used with a range of transition metal-catalyzed reactions to construct simple rotaxanes with macrocycles threaded onto a single axle. However, since the transition metal catalyst/template does not bind more strongly to the product than the starting material, it can in some cases[9a,c−e] turn over during the reaction. It seemed possible that by positioning the ligand at the junction between two macrocycle cavities the single template site might be able to direct active template reactions through each ring. Indeed, our investigation showed that two axles could be successfully threaded in this way, either by forming them using the same reaction (e.g., the Cu(I)-catalyzed azide−alkyne cycloaddition—the CuAAC reaction[10]) or via two different reactions which utilize different transition metal ions (the CuAAC reaction and a Pd(II)-catalyzed alkyne homocoupling[11]).

Results and Discussion

Macrobicyclic [3]Rotaxanes with Identical Axles. The synthesis of doubly threaded [3]rotaxanes is significantly compli-

† University of Edinburgh.
‡ University of St. Andrews.

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cated by the sheer size of the "stoppers" required to prevent dethreading of large rings.[2r,u,12] When contemplating how to achieve multiple threading with active template reactions that turn over, we were intrigued by the idea of incorporating the ligating site within a flexible bridging unit that bisected a large macrocycle into a bicyclic system. This should allow the ligand to orient the metal ion toward each cavity in turn, catalyzing covalent bond formation between appropriately derivatized building blocks through each cavity, producing [3]rotaxanes (Figure 1).

Bicyclic macrocycle **1a** (Scheme 1 and Figure 2) incorporates a 2,6-disubstituted pyridine unit (previously employed as the ligating motif in the active template synthesis of simple [2]rotaxanes[9a,c−e]) in a bridge separating two identical cavities. CPK models indicated that with C_{14} alkyl chains ($n = 2$, Scheme 1) the rings should be large enough to accommodate a thread unit through each cavity while a tris(*tert*-butyl)-substituted trityl group should be a sufficiently large stoppering group to prevent dethreading. The synthesis of **1a** was achieved in eight steps from the commercially available dimethyl acetal of 2,6-dihydroxylbenzoic acid (for details of the synthesis see the Supporting Information). Single crystals of a metal-coordinated

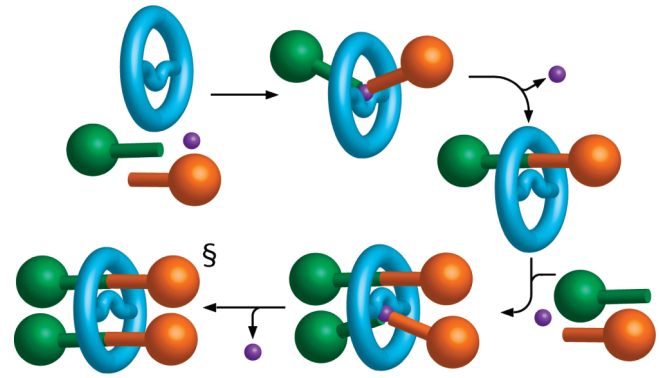

Figure 1. Active template synthesis of macrobicyclic [3]rotaxanes. The metal (purple) coordinates to the binding site. The metal can then promote formation of a covalent bond through each cavity of the macrocycle in turn, generating a doubly threaded [3]rotaxane. If the second thread forms significantly more slowly than the first (negative allostery), then the reaction can effectively be stopped at the intermediate [2]rotaxane stage and a different set of building blocks or even a different metal employed in a different active template reaction to form the second thread of the macrobicyclic [3]rotaxane. §If the threads being formed are not symmetrical through the mirror plane formed by the macrocycle, two different diastereoisomers (syn and anti arrangements of the threads) can be formed even though the threads themselves may be constitutionally identical.

1a complex suitable for X-ray analysis were obtained by slow cooling of a saturated solution of **1a**·$PdCl_2$(MeCN) in acetonitrile and the solid state structure (Figure 2) clearly shows the metal center orienting its chloride ligands so that they protrude through opposite sides of one of the macrocyclic cavities, as required by a rotaxane-forming active template mechanism.[9]

Carrying out the CuAAC reaction[9a,d] between alkyne **2** and azide **3** (5 mol equiv of each) with a stoichiometric quantity of $CuPF_6$ and bicyclic macrocycle **1a** in 1,2-dichloroethane at 70 °C over 24 h generated [2]rotaxane **5a**, which was isolated in 41% yield after demetalation with a basic ethylenediaminetetraacetic acid−ammonia (EDTA−NH_3) solution (Scheme 1; Table 1, entry 1). However, despite using a large excess of the alkyne and azide building blocks, only a small amount (≤10%)

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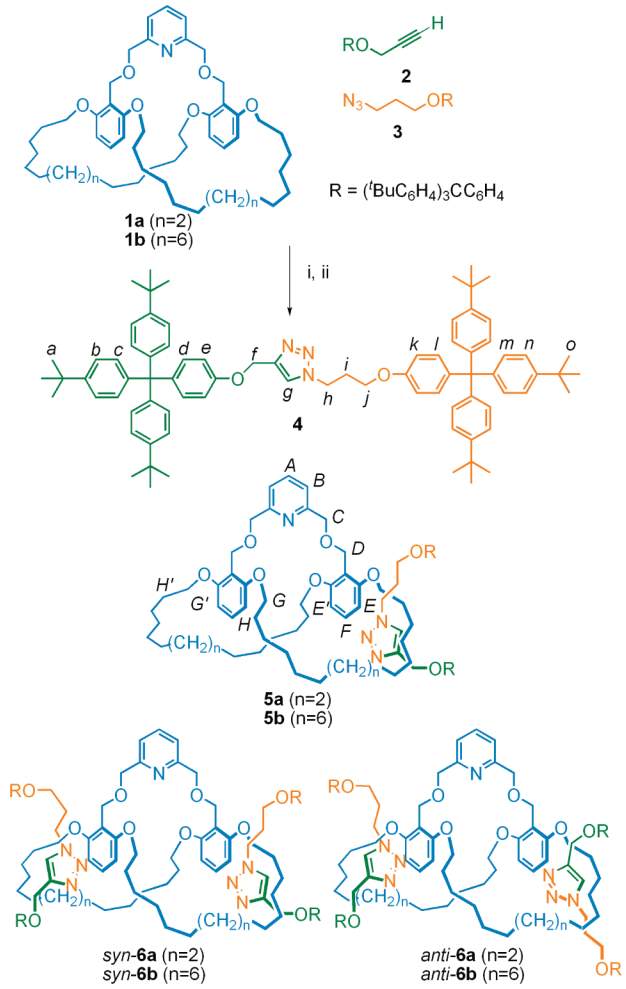
Scheme 1. Synthesis of Macrobicyclic [2]- and [3]Rotaxanes via an Active Template CuAAC Reaction[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 °C; (ii) EDTA, NH_3.

of the accompanying [3]rotaxane **6a** was formed (Table 1, entry 1). It seemed that the low yield of [3]rotaxane **6a** might be a result of the second cavity becoming too congested to accommodate a threading reaction following formation of [2]rotaxane **5a**. We therefore synthesized macrocycle **1b** (see Supporting Information), which possessed an additional four methylene units in each of the macrocyclic rings. Pleasingly, treating this larger bicyclic structure (**1b**) with $CuPF_6$ and 5 mol equiv (2.5 equiv per macrocycle) of **2** and **3** furnished [2]rotaxane **5b** in 57% yield together with 40% of [3]rotaxane **6b**, a combined 97% yield of interlocked products (Table 1, entry 2). Following further addition of azide and alkyne (5 equiv of each), the yield of [3]rotaxane **6b** was increased to 86% (Table 1, entry 3).

The structures of the [2]- and [3]rotaxanes were established unambiguously by mass spectrometry and NMR spectroscopy

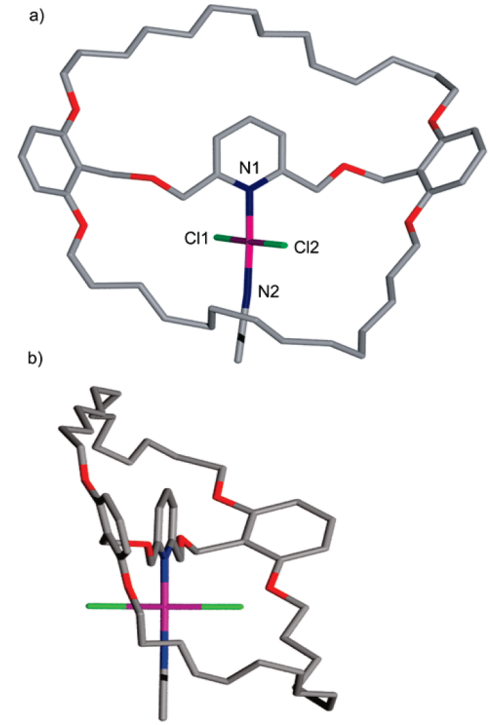


Figure 2. X-ray crystal structure of **1a**·$PdCl_2$(MeCN), from a single crystal obtained by slow cooling of a saturated acetonitrile solution. Nitrogen atoms are shown in blue, oxygen atoms are red, chlorine atoms are green, and palladium is pink. Selected bond lengths (Å) and angles (deg): N1−Pd, 2.02; N2−Pd, 2.01; Cl1−Pd, 2.28; Cl2−Pd, 2.29; Cl1−Pd−Cl2, 178.0. Structure viewed (a) in the plane of the pyridine ring and (b) to show the Cl1−Pd−Cl2 axis directed through one of the macrocyclic rings.

Table 1. Conversion of **1a** and **1b** to Macrobicyclic [2]-and [3]Rotaxanes (Scheme 1)

entry	macrocycle	equiv **2** and **3**	[2]rotaxane yield[a]	[3]rotaxane yield[a]
1[b]	**1a**	5.0	41% (**5a**)	≤10% (**6a**)[c]
2[b]	**1b**	5.0	57% (**5b**)	40% (**6b**)
3[d]	**1b**	10.0[e]	14% (**5b**)	86% (**6b**)

[a] Yields based on macrocycle **1**. [b] Reaction carried out over 24 h. [c] Yield determined by ^{1}H NMR. [d] Reaction carried out over 48 h. [e] Five equivalents of each of **2** and **3** was introduced at the start of the reaction and again after 24 h.

(see Supporting Information). Comparison of the ^{1}H NMR spectrum of [2]rotaxane **5b** (Figure 3b) with those of its noninterlocked components (macrocycle **1b** and thread **4**; Figure 3 panels a and d, respectively) shows upfield shifts of protons of the axle (H_f, H_h, and H_k) and macrocycle (H_A, H_E, and H_G) arising from these regions of the mechanically threaded components spending significant amounts of time face-on to aromatic rings. As only one of the two macrocycle cavities is threaded by an axle in [2]rotaxane **5b**, the bicyclic host is desymmetrized with respect to the parent compound **1b** (Figure 3a) and the ^{1}H NMR spectrum of the [2]rotaxane is correspondingly more complex (note, for example, H_C, H_D, and H_E in

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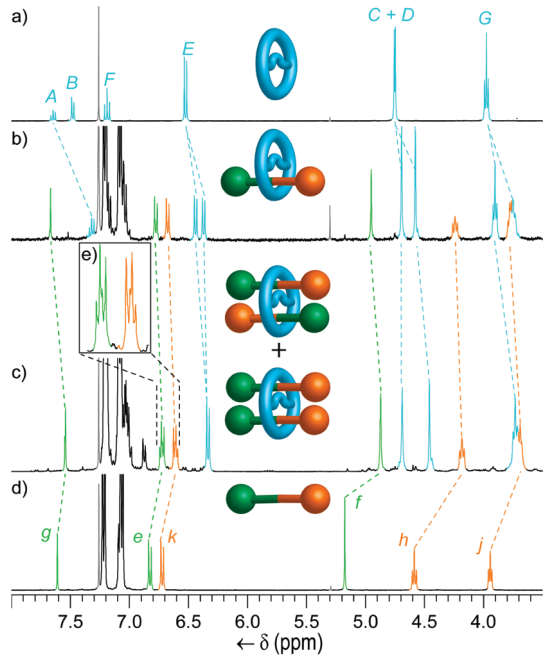
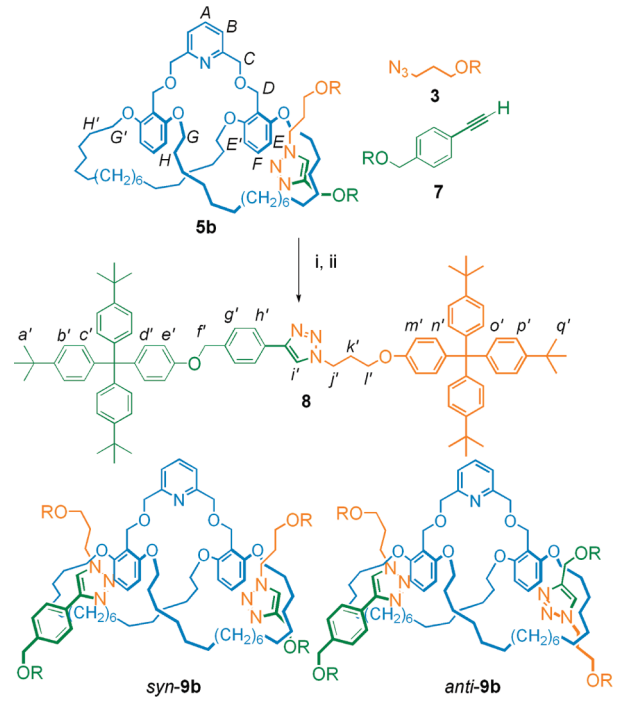


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) macrocycle **1b**, (b) [2]rotaxane **5b**, (c) [3]rotaxane *syn/anti*-**6b**, (d) noninterlocked thread **4**, and (e) expansion of the region showing resonances H_e and H_k in [3]rotaxane *syn/anti*-**6b**. The lettering corresponds to that shown in Scheme 1.

Figure 3b cf. Figure 3a). Penetration of axles through both macrocycle cavities in [3]rotaxane **6b** simplifies the ^{1}H NMR spectrum compared to that of [2]rotaxane **5b**, and the H_E and H_G protons associated with each cavity produce coincident resonances (Figure 3c). This is in spite of the potential for stereoisomerism present in [3]rotaxane **6b**, which can exist as both syn or anti diastereomers depending on whether the axles are threaded in the same direction (syn isomer) through the cavities or in opposite directions (anti isomer), both of which would be expected to be produced in the [3]rotaxane-forming reaction (Scheme 1). Although we could not find HPLC conditions under which the isomers of **6b** were resolved, close examination (Figure 3e) of the signals corresponding to H_e and H_k reveals that they both appear as doubled sets of signals in [3]rotaxane **6b**, suggesting that both stereoisomers are indeed present in the [3]rotaxane reaction product but that they are almost indistinguishable by ^{1}H NMR.

Macrobicyclic [3]Rotaxanes with Different Axles Assembled by Successive Active Template CuAAC Reactions. We next investigated whether the single template site could be used sequentially for the synthesis of [3]rotaxanes in which the thread components are nonidentical. The slower formation of the axle through the second cavity (a form of negative allosteric regulation[13]) of **5b** allows the [2]rotaxane to be isolated in good

Scheme 2. Synthesis of a [3]Rotaxane with Two Different Triazole Threads via Successive CuAAC Active Template Reactions[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 °C; (ii) EDTA, NH_3. 43%.

yield (Table 1, entry 2). Carrying out a second active template CuAAC reaction on this [2]rotaxane intermediate utilizing alkyne **7** in place of alkyne **3** (Scheme 2) generated [3]rotaxane *syn/anti*-**9b,** with different triazole axles threaded through the two macrocycles, in 43% yield (Scheme 2). In the ^{1}H NMR spectrum of *syn/anti*-**9b** (Figure 4b) the formation of the second mechanical bond with a different (unsymmetrical) thread does not give a simplified spectrum of the bicyclic macrocycle component in the manner observed for **6b** (Figure 3c), with the signals corresponding to H_E, for example, clearly arising from two chemically different sets of protons.

Macrobicyclic [3]Rotaxanes with Different Axles Assembled Using Two Different Chemical Reactions. Finally, we attempted the synthesis of [3]rotaxanes using two different active template reactions (catalyzed by different transition metals) to sequentially assemble the two threads via the single template site. A Pd(II)-catalyzed alkyne homocoupling[11] was selected as the second axle-forming reaction as it has previously been successfully used[9e] to assemble simple [2]rotaxanes via active template syntheses using a 2,6-disubstituted pyridine unit as the ligating group. However, when [2]rotaxane **5b** was subjected to these reaction conditions with alkyne **10**, no [3]rotaxane was detected in the reaction mixture. We reasoned that this could be because

(7) For examples of rotaxanes featuring covalently-linked "handcuff"-type macrocycles, see: (a) Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. *Science* **2004**, *303*, 1845–1849. (b) Arico, F.; Chang, T.; Cantrill, S. J.; Khan, S. I.; Stoddart, J. F. *Chem.—Eur. J.* **2005**, *11*, 4655–4666. (c) Loeb, S. J.; Tramontozzi, D. A. *Org. Biomol. Chem.* **2005**, *3*, 1393–1401. (d) Badjić, J. D.; Ronconi, C. M.; Stoddart, J. F.; Balzani, V.; Silvi, S.; Credi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1489–1499. (e) Aprahamian, I.; Olsen, J. C.; Trabolsi, A.; Stoddart, J. F. *Chem.—Eur. J.* **2008**, *14*, 3889–3895. (f) Baytekin, B.; Zhu, S. S.; Brusilowskij, B.; Illigen, J.; Ranta, J.; Huuskonen, J.; Russo, L.; Rissanen, K.; Kaufmann, L.; Schalley, C. A. *Chem.—Eur. J.* **2008**, *14*, 10012–10028.

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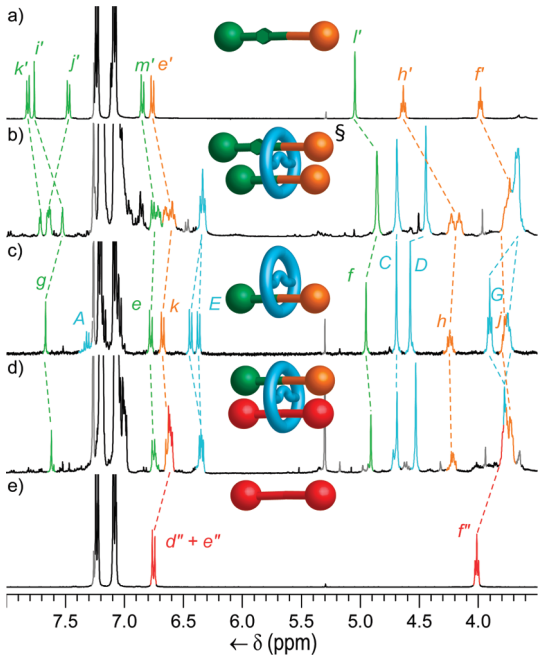
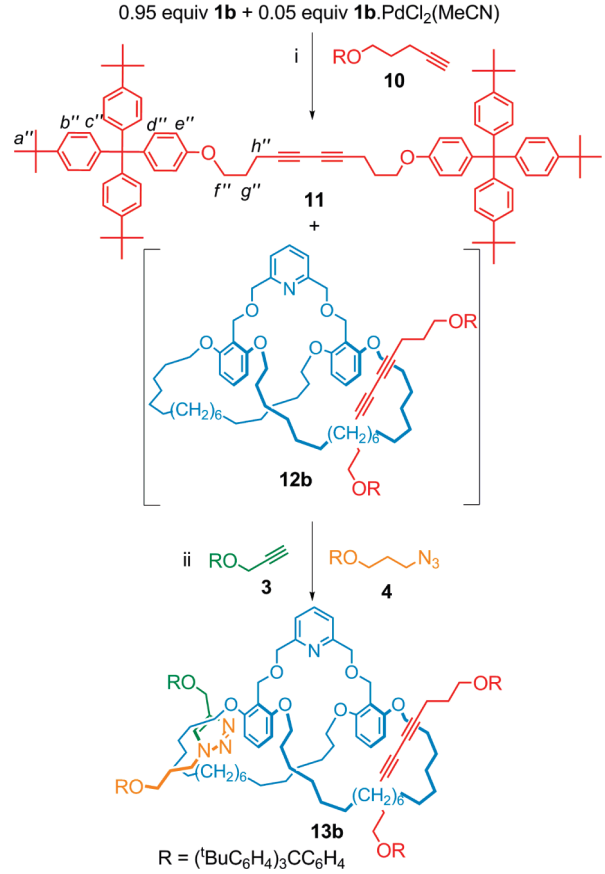


Figure 4. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) noninterlocked thread **8**, (b) mixed-triazole-thread [3]rotaxane *syn*/*anti*-**9b**, (c) [2]rotaxane **5b**, (d) bisacetylene-thread-triazole-thread [3]rotaxane **10b** and (e) noninterlocked thread **11**. The lettering corresponds to that shown in Schemes 2 and 3. The [3]rotaxane spectra contain minor impurities that we were unable to fully remove. [§]Mixture of syn and anti isomers.

the triazole ring of the already threaded axle in **5b** could potentially coordinate[14] to the Pd(II) and inhibit the second active template reaction. We therefore tried switching the order in which the axles were formed, attempting to form the threaded axle from the active template Pd(II)-alkyne homocoupling first and then applying the Cu(I)-catalyzed alkyne−azide cycloaddition with fresh alkyne and azide building blocks (Scheme 3).

The reaction sequence was carried out without purification of the intermediate [2]rotaxane (**12b**). Bicyclic macrocycle **1b** was subjected to the Pd(II)-mediated alkyne homocoupling conditions (5 mol % **1b**·$PdCl_2$(MeCN), 30 equiv **10**, iPr$_2$NH, CuI, I_2, benzene) with stoppered alkyne **10**. After 5 days, all the alkyne had been consumed although ^{1}H NMR suggested only ∼10% conversion to the [2]rotaxane, **12b**, which was not isolated. The solution was extracted with Na_4EDTA and filtered to remove residual Pd, and then the reaction vessel was charged with azide and alkyne building blocks **3** and **4** and the Cu(I)PF_6 catalyst and subjected to the CuAAC reaction conditions. [3]Rotaxane **13b**, with both bisacetylene and triazole threads was isolated in 4% yield over these two synthetic steps (Scheme 3). While the yield is certainly modest (largely the result of the Pd(II)-promoted homocoupling being so poor, the second axle is threaded through the [2]rotaxane intermediate **12b** in ∼40% yield), it nonetheless demonstrates that it is possible to direct

Scheme 3. Synthesis of a [3]Rotaxane with Bisacetylene and Triazole Threads via Sequential Active Template Reactions[a]



[a] Reagents and conditions: (i) **10** (30 equiv), diisopropylamine (10 equiv), CuI (2 equiv), I_2 (0.5 equiv), room temp, benzene; (ii) (1) alkyne **3** (5 equiv), azide **4** (5 equiv), $[Cu(CH_3CN)_4]PF_6$, $ClCH_2CH_2Cl$, 70 °C; (2) EDTA, NH_3; 4% yield over both mechanical bond-forming steps: ∼10% for the first (formation of **12b**); ∼40% for the second (formation of **13b**). For full details of experimental procedures see the Supporting Information.

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two different metal-catalyzed reactions sequentially through different (chemically identical) cavities through the action of one bridging ligating group. As with the other rotaxanes reported in this paper, [3]rotaxane **13b** was unambiguously characterized by NMR spectroscopy and mass spectrometry (see Supporting Information). The ^{1}H NMR of [3]rotaxane **13b** (Figure 4d) is not complicated by the diasteroisomerism present in *syn/anti*-**6b** and *syn/anti*-**9b** since the bisacetylene thread component is symmetrical.

Conclusions

We have demonstrated that it is possible for a suitably located ligand to successively promote covalent bond forming reactions through each cavity of a bicyclic structure, a coordinated transition metal ion simultaneously acting as a catalyst and a template for mechanical bond formation each time. Using the CuAAC reaction of azide and alkyne building blocks, the formation of [3]rotaxanes is remarkably effective, proceeding in up to 86% yield (>94% per axle). Even with this first generation system it is possible to form two mechanical bonds with different axles, although this is less efficient (65% per axle using the CuAAC reaction twice), particularly when employing chemical reactions catalyzed by different metal ions (~10% and ~40%, respectively, for a Pd(II)-catalyzed alkyne homocoupling followed by a Cu(I)-catalyzed CuAAC reaction). The ability to form multiple mechanical bonds via a single template site is a potentially significant addition to the toolbox for interlocked molecule assembly. It may prove useful for constructing heterocircuit Borromean rings,[15] for example, (through the use of cleavable bridging ligands) and other currently inaccessible higher order links that require the threading of multiple different axles through large rings.

Acknowledgment. We thank *Syngenta* for a Ph.D. studentship (to P.R.M.). D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society−Wolfson research merit award.

Supporting Information Available: Experimental procedures and spectral data for all compounds and the details of the X-ray analysis of **1a**·$PdCl_2$(MeCN) including cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9080716

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Published on Web 10/06/2009

Active Metal Template Synthesis of [2]Catenanes

Stephen M. Goldup, David A. Leigh,* Tao Long, Paul R. McGonigal, Mark D. Symes, and Jhenyi Wu

School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom

Received August 19, 2009; E-mail: david.leigh@ed.ac.uk

Abstract: The synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu(I) ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure is reported. These "active metal template" strategies employ appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC "click" reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot−Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit (the rings are constitutionally different) [2]catenanes are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit (two identical rings) [2]catenane in 46% yield through a one-pot, double macrocyclization, procedure. Remarkably, <7% of the corresponding noninterlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu(I) as both a template for the catenane and a catalyst for covalent bond formation in the reaction.

Introduction

The synthesis of catenanes and rotaxanes was revolutionized by the application of template-directed syntheses,[1] in which the components are preorganized prior to covalent capture of the interlocked architecture. Although a large number of different types of template-directed reactions have been successfully employed to form rotaxanes in threading-followed-by-stoppering strategies,[1a] "clipping" approaches to rotaxanes and catenanes (involving single or double macrocyclization of ligands, directed by the template)[2] are rather more demanding and have only been demonstrated with a small number of different macrocyclization reaction types. Of these, Williamson ether synthesis,[2] the Huisgen−Meldal−Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC "click" reaction),[3,4] amide or ester bond-forming reactions,[5] ring-closing metathesis,[6] imine bond formation,[1u,6f,7] and metal−ligand coordination[8] are the most commonly used. The effectiveness of these reactions for catenane synthesis lies in their reactive end groups being sufficiently stable in solution to react overwhelmingly in the desired fashion even when accessing the required reaction geometry is a rare event (as it is for the cyclization of large

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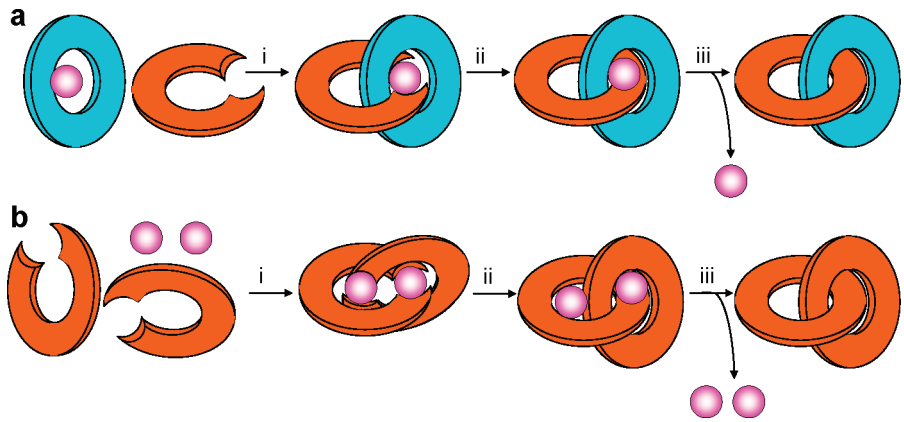

Figure 1. The active metal template approach to catenane synthesis. (a) Single macrocyclization route: (i) Template assembly of a macrocyclic ligand and an acyclic ligand about the metal ion (shown in pink) is followed (ii) by a covalent bond-forming reaction between the end groups of the acyclic ligand, catalyzed by the metal ion, through the cavity of the macrocycle. (iii) Decomplexation affords the metal-free [2]catenane. (b) Double macrocyclization route: (i) Template assembly of the acyclic ligands about one or more metal ions is followed by (ii) successive or simultaneous macrocyclization reactions. (iii) Decomplexation affords the metal-free homocircuit (both macrocycles are the same) [2]catenane. The two routes are analogous to the single and double macrocyclization strategies introduced by Sauvage for the synthesis of catenanes by "passive" metal template methods.[2]

rings), and hence give predominantly macrocyclic products under high dilution. The yield of catenane versus noninterlocked macrocycle then depends on how effectively the template preorganizes the ring-closing reaction to take place while one component is threaded through the cavity of the other.

We recently developed[9] an approach to rotaxane synthesis in which a metal ion ligated endotopically within a macrocycle mediates bond formation between two suitably functionalized building blocks through the macrocycle cavity to assemble the thread. This "active metal template" strategy[9] takes inspiration from ligand couplings employed in transition metal catalysis and opens up a broad range of metal-mediated bond formations for possible use in the synthesis of rotaxanes, the requirement being that the key bond-forming reaction can be directed by the catalyst to proceed through the macrocyclic cavity rather than external to it. Such active metal template processes, where a single species acts as both the template and the catalyst for covalent bond formation, clearly also offer potential for the synthesis of catenanes (Figure 1). Using a metal ion to simultaneously bind to and activate the tethered ends of an acyclic building block to react through the cavity of a macrocycle could lead to reactions with unstable intermediates that would otherwise not lead to interlocked products being used for possible catenane-forming reactions. Active template processes also offer the possibility of traceless assembly[9i] (as the coordinating functional groups are often chemically changed during the reaction into noncoordinating elements) and could be used to prepare catenanes containing multiple rings or having only very weak residual intercomponent interactions, molecules

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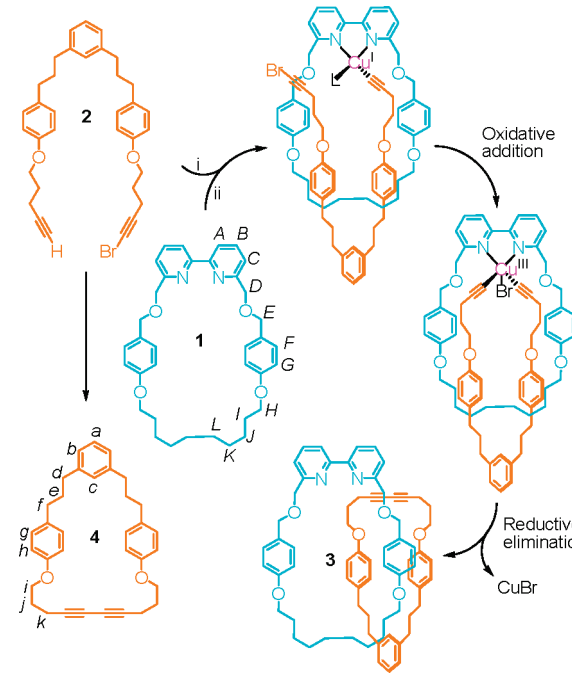
that are often difficult or impossible to achieve with standard template-directed approaches. Here, we report on the application of the active metal template concept to catenane synthesis using both single macrocyclization and double macrocyclization strategies. Heterocircuit (the rings are different) and homocircuit (the rings are the same) [2]catenanes are assembled using appropriately functionalized bidentate pyridine ether or bipyridine ligands and either the Cu(I)-catalyzed CuAAC reaction or the Cu(I)-mediated Cadiot−Chodkiewicz[10] heterocoupling of an alkynyl halide and a terminal alkyne.

Active Metal Template [2]Catenane Synthesis Using the Cadiot−Chodkiewicz Reaction

We initially investigated a modified Cadiot−Chodkiewicz coupling[11] of a bromoalkyne with a terminal alkyne mediated by a Cu^{I} complex of bidentate bipyridyl macrocycle **1**,[9d] due to its efficacy in active template rotaxane-forming reactions.[9g]

Scheme 1. Active Metal Template Cadiot−Chodkiewicz Synthesis of [2]Catenane **3** from Bipyridyl Macrocycle **1** and Alkyne-Bromoalkyne **2**[a]



[a] Reagents and conditions: (i) LiHMDS, THF, −78 °C; (ii) CuI (1 equiv), 5 equiv of **2**, 80 °C, 72 h, 21% (over two steps). L = I, Br, or THF.

Acyclic unit **2** has no potential metal-coordinating sites other than the terminal alkyne and bromoalkyne reactive functional groups and should cyclize to form a ring of similar size and shape to others previously demonstrated to accommodate thread-forming reactions in active template rotaxane syntheses.[9] Building block **2** was treated with LiHMDS ($LiN(SiMe_3)_2$) at −78 °C and then added to a solution of macrocycle **1** and CuI in THF, and the resulting mixture was stirred for 4 days at room temperature (Scheme 1), a procedure similar to that used successfully[9g] for rotaxane formation. However, little of the desired catenane product (**3**) was observed, and only a small amount of **2** was consumed under these conditions. Increasing the reaction concentration, raising the reaction temperature to 80 °C, and employing a 5-fold excess of **2** ultimately gave [2]catenane **3** in 21% yield. The proposed mechanism for the active metal template Cadiot−Chodkiewicz catenane synthesis is shown in Scheme 1.[12] The modest yield illustrates how the catenane-forming reaction, in which the reactive end groups must be tethered together, is much more demanding in terms of conformational requirements of the ligands, and probably steric effects, than the equivalent rotaxane-forming reaction (for which nontethered functional groups are reacted through the macrocycle cavity to form the interlocked thread). The yield of

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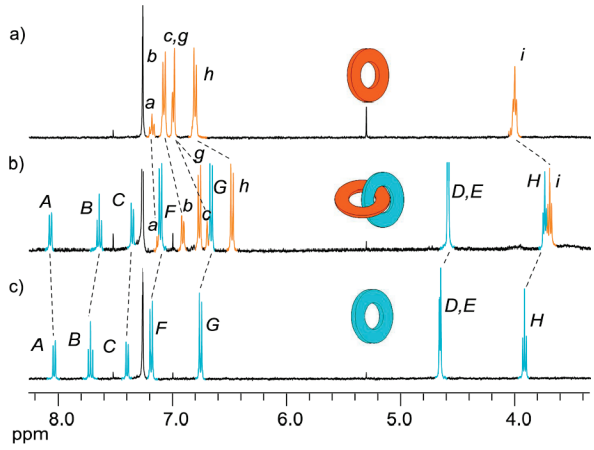


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) bisacetylene macrocycle **4**, (b) [2]catenane **3**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering shown in Scheme 1.

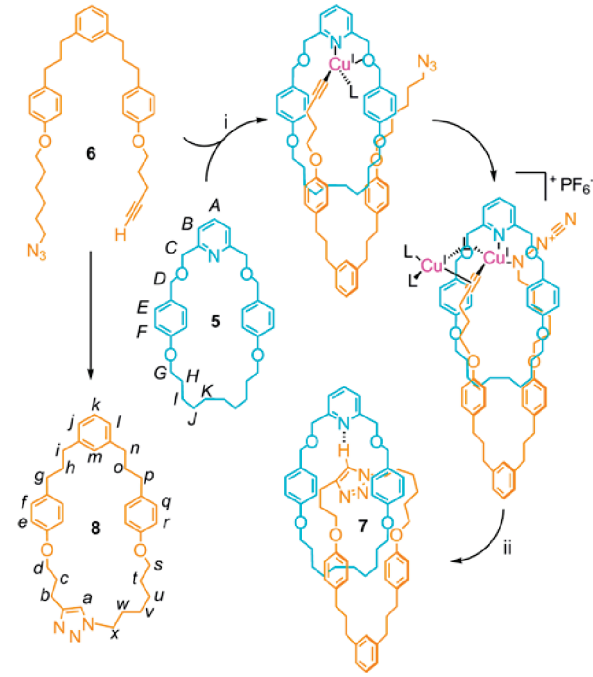
catenane also suffers because the bromoalkyne moiety is present during treatment of the terminal alkyne of **2** with LiHMDS, prior to transmetalation with copper. This leads to some decomposition of the alkyne halide, whereas in the corresponding rotaxane-forming reactions, the terminal alkyne could be treated with LiHMDS and transmetalated with copper before the alkyne halide was added to the reaction mixture.

As a heterocircuit catenane (the two rings are different), the interlocked nature of **3** was apparent from both mass spectrometry (*m*/*z* of the molecular ion) and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of [2]catenane **3** in $CDCl_3$ (Figure 2b) displays upfield shifts of nearly all of the signals with respect to those of the noninterlocked components (Figure 2a and c). Such shielding is typical of interlocked architectures in which the aromatic rings of one component are face-on to another component and is most conspicuous for H_F, H_G, and H_H of macrocycle **1** and H_c, H_h, and H_i of macrocycle **4**. The ubiquity of the upfield shifts implies that the two rings are largely free to rotate with respect to one another, as might be expected in a system where there are no strong intercomponent interactions to stabilize a particular coconformation.

Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Single Macrocyclization Strategy

The qualified success of the catenane-forming active template Cadiot−Chodkiewicz reaction prompted us to try using the CuAAC "click" reaction to form [2]catenanes (Scheme 2, Table 1), a reaction that had also been previously successfully applied to the active template synthesis of rotaxanes[9a,d] and passive template syntheses of both rotaxanes[1t,13] and catenanes.[4] When

Scheme 2. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **7** from Pyridyl Macrocycle **5** and Azide−Alkyne **6**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, CH_2Cl_2, or $C_2H_4Cl_2$; (ii) EDTA, $NH_{3(aq)}$. L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of conditions and reagent stoichiometry on the reaction yield, see Table 1.

Table 1. Influence of Reaction Conditions and Reagent Stoichiometry on the Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenanes **7** and **9** (Schemes 2 and 3)[a]

entry	macrocycle (concentration)	equiv of **6**	*T*/°C	time/h	conversion to triazole products (%)	yield (%) of [2]catenane **5**→**7** **1**→**9**
1[a]	**5** (6.5 mM)	1	RT	24	15[b]	<5[b]
2	**5** (6.5 mM)	1	80	96	90	16
3	**5** (6.5 mM)	5	80	240	>98	25
4	**5** (1.25 mM)	5	80	288	>98	53
5	**1** (1 mM)	5	80	500	50	50
6	**1** (5 mM)	5	80	170	>98	49

[a] One equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to the macrocycle (**1** or **5**). All reactions were carried out in $C_2H_4Cl_2$, except entry 1 (CH_2Cl_2). [b] Yield estimated by ^{1}H NMR.

an equimolar mixture of macrocycle **5**,[14] $[Cu(CH_3CN)_4](PF_6)$, and the acyclic azide−alkyne unit **6** in dichloromethane was stirred for 24 h at room temperature, a low conversion to triazole products was observed with only trace amounts of catenane apparent in the ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 1). Changing the solvent to 1,2-dichloroethane and raising the temperature to 80 °C afforded [2]catenane **7** in 16% yield with near complete conversion of **6** to triazole products (Table 1, entry 2). Finally, by increasing the number of equivalents of **6** relative to **5** and running the reaction at greater dilution (which required extended reaction times), the yield of catenane **7** was increased to a pleasing 53% (Table 1, entry 4). Isolation of the metal-free catenane was facilitated by washing the crude product mixture with a basic EDTA solution.

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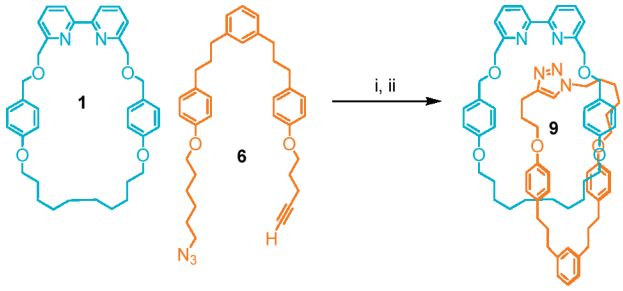
Scheme 3. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **9** from Bipyridyl Macrocycle **1** and Azide−Alkyne **6**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 7−21 d. (ii) EDTA, $NH_{3(aq)}$, 49−50% (over two steps). For the effect of concentration on the time of reaction, see Table 1.

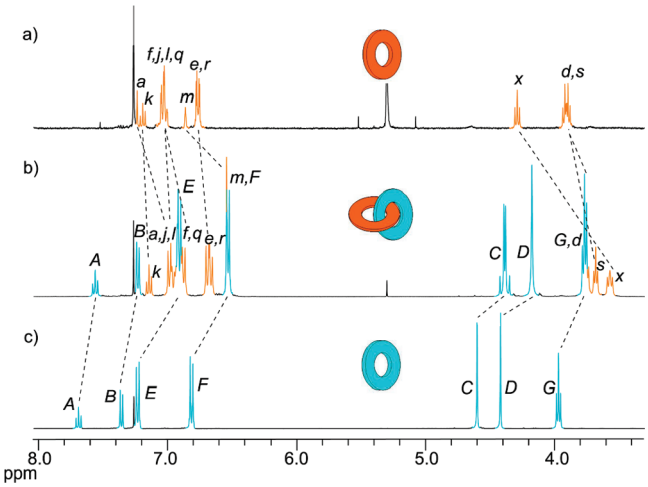


Figure 3. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **7**, and (c) pyridine macrocycle **5**. The assignments correspond to the lettering shown in Scheme 2.

The ^1H NMR spectrum of catenane **7** (Figure 3b) shows significant upfield shifts of various signals (H_x ~0.6 ppm, H_m ~0.4 ppm, H_E ~0.3 ppm, and H_F ~0.3 ppm) with respect to the components (Figure 3a and c), consistent with its interlocked architecture. Interestingly, signals corresponding to H_C appear as an AB system, indicating that the two faces of the pyridyl macrocycle are inequivalent. This is a result of the triazole group making the ring threaded through the pyridyl macrocycle inherently unsymmetrical. The chemical shift of H_a of the triazole group suggests it may form a C−H···N hydrogen bond[15] with the pyridine nitrogen atom of the other macrocycle.

Both pyridyl and bipyridyl macrocycles have been found to undergo efficient active template rotaxane assembly with the CuAAC reaction,[9d] although the kinetics of the reactions are very different (the bipyridyl macrocycle reaction is considerably slower) as a result of the reactions proceeding through different types of intermediates. The same trend was seen with the active template catenane-forming reaction (Scheme 3 and Table 1, entries 5 and 6). Although good yields (49−50%) of [2]catenane **9** could be obtained, they required long reaction times (7−21 days) at 80 °C and/or higher reaction concentrations. It is testimony to the very specific reaction preferences of the azide and alkyne functional groups under Cu(I) catalysis that they survive for so long without undergoing side reactions until the apparently very rare event of the groups being in just the right position to react to form catenane occurs.

(15) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12111–12122.

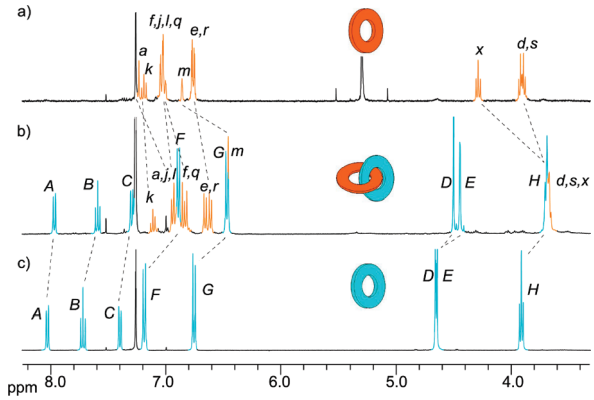


Figure 4. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **9**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering indicated for macrocycles **1** and **8** in Schemes 1 and 2, respectively.

The ^1H NMR spectrum of catenane **9** (Figure 4b) again shows upfield shifts of most of its signals with respect to its noninterlocked components (Figure 4a and c). Signals H_F and H_G of bipyridine macrocycle **1** are each shifted by ~0.2 ppm, consistent with $\pi-\pi$ stacking between the aromatic rings to which H_F and H_G are attached and the aromatic rings of macrocycle **8**. As in catenane **7**, the signals corresponding to H_E appear as an AB system, although this is less pronounced than in the pyridine macrocycle-derived catenane.

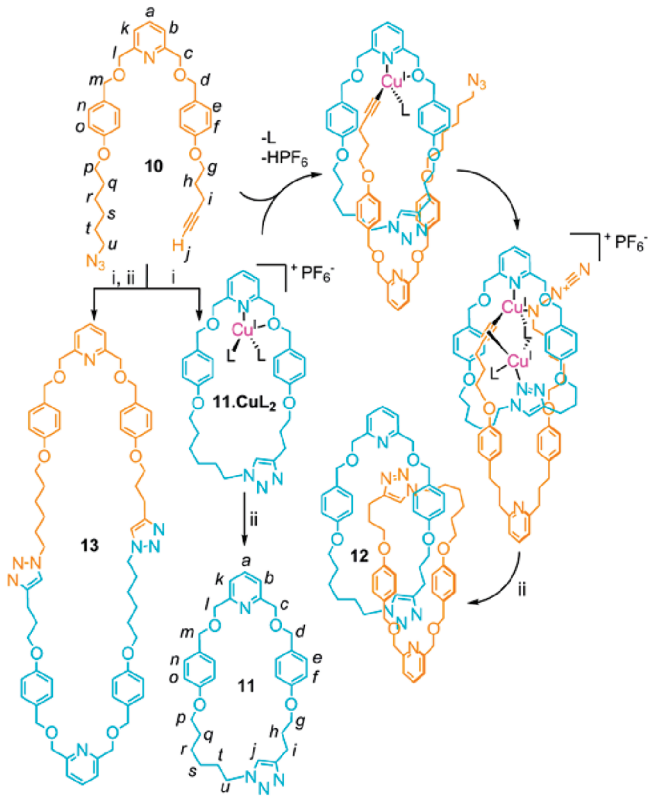
Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Double Macrocyclization of Two Identical Acyclic Building Blocks

The active template reactions investigated so far (Schemes 1−3) featured a preformed macrocycle as one of the components and involved a single macrocyclization step (Figure 1a) leading to heterocircuit catenanes. We were interested to see whether it would be possible to extend this concept to an active template double macrocyclization strategy (Figure 1b) in which a homocircuit (both interlocked rings constitutionally identical) [2]catenane was assembled in one pot by two successive macrocyclization reactions (the final one, at least, having to be templated by the catalyst) of a single type of building block (Scheme 4).

Ligand **10** incorporates the terminal alkyne and azide groups necessary for the CuAAC reaction, together with a pyridine group for coordination to a Cu ion catalyzing the ring closure of another molecule of **10**. The covalent framework of the ligand was chosen to mimic macrocycle **5** and acyclic unit **6**, which combine effectively to give catenane in the single macrocyclization active template CuAAC reaction (Scheme 2).

Building block **10** was dissolved in $C_2H_4Cl_2$ with one-half of an equivalent of $[Cu(CH_3CN)_4](PF_6)$, and the solution was heated at 80 °C for 5 days (Scheme 4). The yield of [2]catenane proved to be highly dependent on the reaction concentration (Table 2), presumably a reflection of the delicate balance between various types of coordination complexes that can give rise to oligomers, noninterlocked macrocycles, or catenane. Carrying out the reaction at an initial 0.3 mM concentration of **10** gave a remarkable 46% yield of metal-free [2]catenane **12**, isolated after workup with a basic EDTA solution and purification by column chromatography. Very little (<7% as compared

Scheme 4. Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** from Azide−Alkyne **10**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 5 d. (ii) EDTA, $NH_{3(aq)}$. L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of concentration on catenane yield, see Table 2.

Table 2. Influence of Concentration on the Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** (Scheme 4)[a]

entry	[**10**] (mM)	conversion to triazole products (%)	ratio catenane **12**:macrocycles **11** and **13**	yield of [2]catenane **10**→**12** (%)
1	15	>98	2:3	8
2	6	>98	2:3	16
3	3	>98	5:2	25
4	1	>98	3:1	30
5	0.3	>98	7:1	46
6	0.08	65	1:1	40
7	0.03	25	1:6	6

[a] One-half of an equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to **10**. All reactions were performed in $C_2H_4Cl_2$ at 80 °C over 120 h.

to 46% [2]catenane) of noninterlocked macrocycles **11** and **13** were isolated from the reaction reported in Table 2, entry 5. It is intriguing that even at these relatively low concentrations the double macrocyclization reaction is more selective for the [2]catenane than the corresponding single macrocyclization employing pyridine macrocycle **5** and 1 equiv of the acyclic azide−alkyne building block **6** (Scheme 2 and Table 1, entry 2). A possible explanation could be that the second Cu(I) ion involved in the mechanism of these reactions[3,9d] becomes coordinated to the triazole nitrogen of macrocycle **11**, resulting

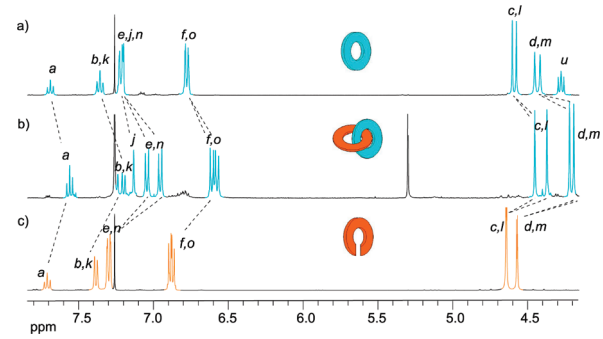


Figure 5. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) macrocycle **11**, (b) [2]catenane **12**, and (c) azide−alkyne building block **10**. The assignments correspond to the lettering shown in Scheme 4.

in a reaction geometry in which interlocking is significantly enhanced, as shown in Scheme 4. As the two Cu(I) centers are linked via both a bridging ligand, L, and coordination to the alkyne, the azide is forced to approach the reactive center through the cavity of macrocycle **11** for the CuAAC reaction to occur, leading predominantly to catenane.

The structure of [2]catenane **12** was confirmed by mass spectrometry (fragmentation and MS−MS studies) and ^1H NMR spectroscopy. The ^1H NMR spectrum of catenane **12** in $CDCl_3$ is shown in Figure 5b. The upfield shifts of the signals as compared to macrocycle **11** (Figure 5a) and building block **10** (Figure 5c) show the same general trends found in the heterocircuit catenane produced by the single macrocyclization active template CuAAC reaction, **7** (Figure 3).

Conclusions

The active template concept developed for rotaxanes can be successfully extended to the more demanding requirements of catenane synthesis. Heterocircuit [2]catenanes were prepared in 21−53% yields through Cu(I)-mediated active template single macrocyclization strategies employing the Cadiot−Chodkiewicz (forming a symmetrical bisacetylene-containing macrocycle) or CuAAC "click" reaction (forming an unsymmetrical triazole-containing macrocycle) and preformed monodentate or bidentate macrocyclic ligands. The CuAAC reaction could also be used to assemble homocircuit [2]catenanes from a single type of acyclic building block in a one-pot procedure in up to 46% yield, a remarkable catalytic assembly reaction notable for its selectivity for the interlocked architecture over noninterlocked macrocyclic products. The application of such strategies to higher order interlocked structures is currently under investigation in our laboratory.

Acknowledgment. We thank Juraj Bella for assistance with the high field ^{13}C NMR studies and Syngenta for a Ph.D. studentship (to P.R.M.). D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society-Wolfson research merit award.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9070317